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This report is required by law (7 USC 2143) Failure to report according to the regulations can result in an order to cease and desist and to be subject to penalties as provided for in Section 2150

Set reverse side for additionalinformation

Interagency Report Control No
0180-DOA-AN

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

1. REGISTRATION NO.
14-R-0144 #1799

FORM APPROVED
OMB NO. 0579-0036

ANNUAL REPORT OF RESEARCH FACILITY
(TYPE OR PRINT)

2. HEADQUARTERS RESEARCH FACILITY (Name and Address, as registered with USDA include Zip Code)

Charles River Labortories, Inc
251 Ballardvale Street
Wilmington, MA 01887
781-222-6000

3. REPORTING FACILITY (List all locations where animals were housed or used in actual research, testing, teaching, or experimentation, or held for these purposes. Attach additional sheets if necessary.)

FACILITY LOCATIONS (Sites) See Attachment #1

REPORT OF ANIMALS USED BY OR UNDER CONTROL OF RESEARCH FACILITY (Attach additional sheets if necessary or use APHIS FORM 7023A)

A. Animals Covered By The Animal Welfare Regulations	B. Number of animals being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not yet used for such purposes	C. Number of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use of pain-relieving drugs.	D. Number of animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic, or tranquilizing drugs were used	E. Number of animals upon which teaching experiments, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which the use of appropriate anesthetic, analgesic, or tranquilizing drugs would have adversely affected the procedures, results, or interpretation of the teaching, research, experiments, surgery, or tests. *(An explanation of the procedures producing pain or distress in those animals and the reasons such drugs were not used must be attached to this report)*	F. TOTAL NO OF ANIMALS (Cols. C + D + E)
4. Dogs	93	1971	676	130	2777
5. Cats					
6. Guinea Pigs	133	2833	2679	36	5548
7. Hamsters	275	1564	761	6	2331
8. Rabbits	1230	5433	856	834	7123
9. Non-human Primates	3564	2923	1523	7	4453
10. Sheep			12		12
11., Pigs	30	623	184	8	815
12. Other Farm Animals					
13 Other Animals					
Cotton Rats	2	8	1		9
Gerbils		122			122

ASSURANCE STATEMENTS

1) Professionally acceptable standards governing the care, treatment, and use of animals including appropriate use of anesthetic, analgesic, and tranquilizing drugs, prior to, during and following actual research, teaching, testing, surgery, or experimentation were followed by this research facility

2) Each principal investigator has considered alternatives to painful procedures.

3) This facility is adhering to the standards and regulations under the Act, and it has required that exceptions to the standards and regulations be specified and explained by the principal investigator and approved by the Institutional Animal Care and Use Committee (IACUC). A summary **of all such exceptions is attached to this annual report.** In addition to identifying the IACUC-approved exceptions, this summary includes a brief explanation of the exceptions, as well as the species and number of animals affected.

4) The attending veterinarian for this research facility has appropriate authority to ensure the provision of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use.

CERTIFICATION BY HEADQUARTERS RESEARCH FACILITY OFFICIAL

(Chief Executive Officer or Legally Responsible Institutional Official)

I certify that the above is true, correct, and complete (7 U.S.C. Section 2143).

(B)(6) (B)(7)(c)

DATE SIGNED
1-18-2008

APHIS FORM 7023 (AUG 91) (Replaces VS FORM 18-23 (OCT 88) which is obsolete

Charles River Laboratories
Customer #: 1799
USDA Research Registration #14-R-0144

Attachment #1

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Site #	Location Description
002	**Charles River Laboratories Research Models & Services** (b)(2) High and B(7)(F)
003	**Charles River Laboratories Preclinical Services** (b)(2) High and B(7)(F) **(Southbridge) Deleted from Research Registration on 12/1/2006**
005	**Charles River Laboratories Preclinical Services -** (b)(2) High and B(7)(F)
013	**Charles River Laboratories Preclinical Services** (b)(2) High and B(7)(F) **(Worcester) Deleted from Research Registration on 9/21/2007**
014	**Charles River Laboratories Preclinical Services** (b)(2) High and B(7)(F)
016	**Charles River Laboratories Preclinical Services** (b)(2) High and B(7)(F)
017	**Charles River Laboratories Preclinical Services** (b)(2) High and B(7)(F)
018	**Charles River Laboratories -** (b)(2) High and B(7)(F)
020	**Charles River Laboratories Consulting & Staffing Services** b2 high, b7F
021	**Charles River Laboratories Research Models & Services -** (b)(2) High and B(7)(F)
022	**Charles River Laboratories Preclinical Services** (b)(2) High and B(7)(F) **(Shrewsbury) Added to Research Registration on 12/1/2006**

Preface:

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Animals placed in Column "E" in this report were utilized in Preclinical Services Facilities (listed above) belonging to Charles River Laboratories . These animals were enrolled in studies undertaken for product registration purposes based on regulatory guidelines of the FDA 21 CFR 312.23 for pharmacology and toxicology studies and the Red Book. Guidance for study design and conduct also conformed with recommendations by the International Conference on Harmonization Guidelines. This guidance includes Part VII, DHHS, FDA, International Conference on Harmonization; Guidance on non-clinical safety studies for the conduct of human clinical trial for pharmaceuticals, Federal Register, Vol. 62, #227, November 25, 1997.

Depending upon the nature of the compound, certain other regulations and guidelines promulgated by the FDA, EPA, TSCA, FIFRA and the OECD also apply and are listed in the Applicable Guidelines/Regulations section below.

Animals could be placed in Category "E" both prospectively and retrospectively. The majority of categorization was done by retrospective analysis. Retrospective categorization of pain or distress was made by the Attending Veterinarian (or their designee, also a laboratory animal veterinarian) in conjunction with the Study Director. Professional judgment calls, particularly with regard to the diagnosis of distress, were purposely conservative with a default of category E if there was any doubt.

The following are applicable guidelines and regulations covering the conduct of studies at all Charles River Laboratory Preclinical Services facilities (listed below).

- Redbook 2000 Toxicological Principles for the Safety Assessment of Food Ingredients, November 2003.
- PART VII, DHHS, FDA, International Conference on Harmonization; Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trial For Pharmaceuticals, Federal Register, Vol. 62, No. 227, Nov 25, 1997
- EPA Health Effects Test Guidelines OPPTS 870.3050, 28-Day Oral Toxicity in Rodents, July 2000
- EPA Health Effects Test Guidelines OPPTS 870.3150, 90-Day Oral Toxicity in Non-Rodents, August 1998
- EPA Health Effects Test Guidelines OPPTS 870.3100, 90-Day Oral Toxicity in Rodents, August 1998
- EPA Health Effects Test Guidelines OPPTS 870.4100, Chronic Toxicity, August 1998
- EPA Health Effects Test Guidelines OPPTS 870.3500, Preliminary Developmental Toxicology Screen, March 1994
- EPA Health Effects Test Guidelines OPPTS 870.3600, Inhalational Developmental toxicity Study March 1994
- EPA Health Effects Test Guidelines OPPTS 870.3700, Prenatal Developmental Toxicity Study, August 1995
- EPA Health Effects Test Guidelines OPPTS 870.3800, Reproduction and Fertility Effects, August 1995
- OECD Guideline for the Testing Of Chemicals, Repeated Dose 90-day Oral Toxicity Studies in Non-Rodents, 409, September 1998
- OECD Guideline for the Testing Of Chemicals, Repeated Dose 90-day Oral Toxicity Studies in Rodents, 408, September 1998
- OECD Guideline for the Testing Of Chemicals, Repeated Dose 28-day Oral Toxicity Studies in Rodents, 407, July 1995

- U.S. Food and Drug Administration (1994). International Conference on Harmonization; Guideline on detection of toxicity to reproduction for medicinal products. *Federal Register*, September 22, 1994, Vol. 59, No. 183.
- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- Japanese Ministry of Health, Labour and Welfare (1997). Good Laboratory Practice Standard for Safety Studies on Drugs, MHW Ordinance Number 21, March 26, 1997.
- Organisation for Economic Co-operation and Development (1998). The Revised OECD Principles of Good Laboratory Practices [C(97) 186/Final].
- U.S. Food and Drug Administration (2003). *Guidance for Industry - Photosafety Testing,* Center for Drug Evaluation and Research (DCER), May 2003
- Organisation for Economic Co-operation and Development (1987). *Guidelines for Testing of Chemicals.* Section 4, No. 402: Acute Dermal Toxicity, pp. 1-7
- Organisation for Economic Co-operation and Development (1992). *Guidelines for Testing of Chemicals.* Section 4, No. 406: Skin Sensitization, pp. 1-9.
- *Drug Registration Requirements in Japan,* 4th Edition (19910. Yakuji Nippo, Ltd., Tokyo, pp. 61-64.
- U.S. Food and Drug Administration (2005) Investigational New Drug Application, Title 21, Part 321.23, 8.ii.a
- Organisation for Economic Co-operation and Development (1998). The Revised OECD Principles of Good Laboratory Practices [ENV/MC/CHEM(98)17]
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry; detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD).
- Pharmaceutical Affairs Bureau, Ministry of Health, Labour and Welfare, GLP standard ordinance for non-clinical laboratory studies on safety of drugs, MHW Ordinance No. 21; March 26, 1997. Japan.
- OECD Environment Directorate. OECD Principles of Good Laboratory Practices, [C(97) 186/Final] (1998); Environmental Health and Safety Division
- U.S. Food and Drug Administration (1993). Points to consider in the characterization of cell lines used to produce biologicals.
- European Pharmacopoeia Monograph 5.2.3, Cell substrates for production of vaccines for human use. 01/2005:50203
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry; toxicokinetics: the assessment of systemic exposure in toxicity studies, ICHS3A; March, 1995, Rockville (MD).
- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, MD(R1) Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals.

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REVIEW OF CATETORY "E" STUDIES

The following studies have been listed in Category "E" based upon the guidelines stated in the preface at the beginning of this report. The study designs that resulted in certain animals being placed retrospectively into Category "E" were required by federal regulations and guidelines listed in the applicable regulations/guidelines section below. For the purpose of this report studies have been given a unique number that corresponds to the actual study number. For reasons of confidentiality, actual study numbers are not presented but are available to the USDA for on-site inspection or report follow-up. Category "E" explanations/details are listed separately for each study.

CHARLES RIVER LABS PRECLINICAL SERVICES– (Pennsylvania - Site #014)

Study: #1

Animals: 3 Rabbits

Type of Study: Intravenous Dosage-Range Developmental Toxicity Study of XXXX in Rabbits

Guidelines/Regulations:

This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Three rabbits** from this dosage range-finding study currently being conducted (September 21, 2007- October 18, 2007) have been placed in category E due to potential distress that may be associated with the effects of the test article. The rabbits are currently being dosed once daily intravenously from gestation day 7 through 19.

#3171 (100 MKD), #3174 (100 MKD) and #3175 (100 MKD) had severely reduced feed intake for 5 days beginning on the first day of dosage and lost 6 to 9% body weight during this time. Scant feces and un-groomed coat are also present while the animals remain bright, alert and inquisitive. A second water source and a supplemental food item (timothy cubes) were provided. As of September 30, eight more days of dosage remain. Although the rabbits appear clinically normal (bright, alert, active and inquisitive), it is possible that some discomfort/distress from test article exposure resulted in the decreased feed intake, therefore, these rabbits have been categorized as E.

Study: #2

Animals: 3 Rabbits

Type of Study: Oral (Gavage) Developmental Toxicity Study in Rabbits

Guidelines/Regulations:

- U.S. Food and Drug Administration. Good Laboratory Practice Regulations; Final Rule. 21 CFR Part 58; last revised April 1, 2002; U.S. Federal Government Archives.
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95. This study evaluates ICH Harmonised Tripartite Guideline stages C and D of the reproductive process.
- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of

toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD) Federal Register, September 22, 1994, Vol. 59, No. 183.

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Diagnosis: **Three rabbits** from this developmental toxicity study conducted in September-October 2006 have been placed in category E as described in the paragraphs below.

Rabbit #9026 (II; 3 MKD) was found dead at 10:35 a.m. on gestation day 11 prior to dosage administration that day. There was no indication of adverse signs at the time of the morning viabilities check conducted 2.5 hours earlier. No adverse signs were recorded as present on any of the days prior to the death. 17.9% body weight was lost from GD6-10. Feed intake was a moderate level on GD6-7 and low from GD7 until death. This animal is placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

Rabbit #9044 (III; 10 MKD) was found dead at 1:24 p.m. on gestation day 11 approx. 3 minutes after attempted dosage administration. This rabbit was normal prior to this event. Necropsy exam revealed that the cause of death was a result of a gavage error. While the duration of time between dosing and death may be short, this animal has been placed in category E acknowledging that it could be considered more than a momentary period of pain/distress.

Rabbit #9064 (IV; 30 MKD) lost 13.8% body weight over 14 days and had low feed intake for 9 days. At initial examination, the rabbit was bright, alert, responsive, inquisitive and well groomed. Daily grooming was started to remove loose hair that could be ingested during self-grooming and a timothy cube was provided daily as an alternative food source. At each of the three re-exams, body weight was gained, feed intake had improved and the timothy cube was consumed. The rabbit was euthanized as scheduled at the end of the study. Although the rabbits appear clinically normal (bright, alert, active and inquisitive), it is possible that some discomfort/distress from test article exposure resulted in the decreased feed intake, therefore, these rabbits have been categorized as E.

Study: #3
Animals: 6 Hamsters
Type of Study: Subcutaneous, Single-Dose Tolerability Dose Range Finding Study of XXX in Neonatal Hamsters [1-2 Days Old], With an Observation Period of Fourteen Days

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on the U.S. Food and Drug Administration's Center for Biologics Evaluation and Research (CBER): Guidance for Industry, Considerations for Plasmid DNA Vaccines for Infectious Disease Indications (February 2005, U.S. Dept. of Health and Human Services/FDA).
- U.S. Food and Drug Administration (1883). Points to consider in the characterization of cell lines used to produce biologicals.

Diagnosis: Six hamster pups from this tolerability dose range-finding study conducted in March 2007 have been placed in category E as described below.

#8403 (Male; IV) and #8502 (Male; IV) were found dead at viability cheeks on study days 3 and 8, respectively. Weight loss beginning 2 to 4 days prior to death until death (dead body weight), was 13% and 7%, respectively. #8403 had no adverse signs and #8502 had a two day history of dehydration. Both animals were normal at necropsy examination. These animals have been placed in E acknowledging that the weight loss and dehydration may have been associated with distress.

#9305 (Male; IV), #8505 (Male; IV), #8605 (Female; III) and #8509 (Female; IV) were missing and presumed cannibalized on study days 4, 5, 10 and 4, respectively. These animals had no history of body weight loss. All animals except #8509 appeared normal daily. #8509 had a pinpoint scab at each axillary area presumed to be from transport by the dam. These animals have been placed in category E because there is no postmortem information to rule out the possibility of distress prior to death and two other animals in the same dose group had decreased body weight which may have been associated with distress. Since we could not determine definitively is these four hamsters experienced some level of distress prior to death, we have conservatively categorized them as E.

Study: #4
Animals: 4 Rabbits
Type of Study: Two-Week Oral (Gavage) (Once Daily) Reproductive Toxicity Study in

Male Rabbits.

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products & toxicity to male fertility, (ICH) S5(R2); November 2005, Rockville, MD. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full male fertility study, larger numbers of animals may be needed for the full study.

Diagnosis: **Four male rabbits** from this reproductive toxicity study have been placed in category E due to the possibility of distress that may have been associated with the effects of the test article.

The four rabbits were dosed once at 500 mg/kg by stomach tube. The rabbits were checked hourly. At least one clinical sign was observed in each of the four rabbits at more than one of the hourly post check intervals. These included lacrimation, un-groomed fur, decreased activity (two rabbits) and cold-to-touch (two rabbits.) The study was approved to allow rabbits to progress to moribund condition at which time euthanasia could occur. One rabbit was found dead during post checks approximately 8 hours after dosage and was normal at necropsy exam. The remaining three rabbits appeared normal on the day after dosage and were euthanized as part of the study design. These animals were categorized as E because the decreased activity and/or decreased body temperature as indicated by the "cold-to-touch" clinical observation may have been consistent with of some level of discomfort/distress.

Study: #5
Animals: 2 Rabbits
Type of Study: Oral (Gavage) Fertility and General Reproduction Toxicity Study in Male Rabbits

Guidelines/Regulations:

- This study will be conducted in compliance with the Good Laboratory Practice (GLP) regulations of the U.S. Food and Drug Administration (U.S. Food and Drug Administration 21 C.F.R 58).
- OECD Environment Directorate. OECD Principles of Good Laboratory Practices, (C(97)186/Final] (1998); Environmental Health and Safety Division
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95.

Diagnosis: **Two male rabbits** from group III of this fertility and reproductive toxicity study currently in progress (August 2007-November 2207) have been placed in category E due to distress that may have been associated with the effects of the test article.

#3758 (80 MKD) and #3769 (80 MKD) experienced body weight losses of 16% and 12%, respectively, beginning on the first day of dosage administration for 10-12 days. Feed intake was also severely reduced beginning on the first day of dosage administration. After study day 12, body weight was re-gained and feed intake improved to a good level. Reduced fecal output was the only adverse clinical sign in these two rabbits. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss during the first 10-12 days of dosing.

Study: #6
Animals: 25 Rabbits
Type of Study: Oral (Gavage) Fertility and General Reproduction Toxicity Study in Male Rabbits

Guidelines/Regulations:

- This study will be conducted in compliance with the Good Laboratory Practice (GLP) regulations of the U.S. Food and Drug Administration (U.S. Food and Drug Administration 21 C.F.R 58).
- OECD Environment Directorate. OECD Principles of Good Laboratory Practices, (C(97)186/Final] (1998); Environmental Health and Safety Division
- ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products, and Toxicity to Male Fertility S5 (R2). Parent Guideline dated 24 June 1993. Adopted by CPMP, September 93, issued as CPMP/ICH/386/95.

Diagnosis: **Twenty five male rabbits** from group IV of this fertility and reproductive toxicity study conducted in August 2007-September 2007 have been placed in category E due to distress that may have been associated with the effects of the test article.

#3776-#3800 (250 MKD) experienced body weight loss (8-18%) beginning on the first day of dosage administration for at least 6 days or until death. Feed intake was also severely reduced beginning on the first day of dosage administration. At necropsy some of the animals had stomach erosions or ulcers. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

Study: #7
Animals: 3 Rabbits
Type of Study: Vehicle Tolerance and Pharmacokinetic Study for XXX in Rabbits via Oral (Stomach Tube), Intravenous and Subcutaneous Routes

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This study is being done to determine suitability of vehicle formulation for further studies and pharmacokinetics of the test material in NZW rabbits. Future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products & toxicity to male fertility, (ICH) S5(R2); November 2005, Rockville, MD. These guidelines require that dosages produce some level of toxicity in the high dose group. Conducting this study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this study prior to the required full toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Three rabbits** from this vehicle tolerance and pharmacokinetic study have been placed in category E as described below for reduced feed intake and/or other clinical signs.

#9295 (50 MKD stomach tube) had severely reduced feed intake on study days 2-5 and was euthanized as scheduled on study day 5. A 4% body weight loss occurred on study days 1-3 and an un-groomed hair coat was noted on study day 1. . This animal is placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

#9298 (50 MKD subcutaneous) and # 9299 (50 MKD subcutaneous) had feed intake reduced to a low or fair level on study days 2-5 and 6%-10% body weight was lost over the same period. One or two of the six injection sites were discolored (black to red/purple) beginning at the one hour post check on the first day of dosage through scheduled euthanasia on study day 5. No other adverse clinical observations were noted. The skin discoloration is presumed to be bruising as a result of the manual tenting of the skin for the injection procedure since the skin did not appear otherwise irritated by the test article and because the other rabbits in this group had normal skin throughout the study. . These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

Study: #8
Animals: 12 Rabbits
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study of XXX in Rabbits

Guidelines/Regulations:

- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD).
- U.S. Food and Drug Administration. Good laboratory practices for nonclinical laboratory studies, 21 C.FR 58.
- Pharmaceutical Affairs Bureau, Ministry of Health, Labour end Welfare. OLP standard ordinance for nonclinical laboratory studies on safety of drugs, MHW Ordinance No. 21; March 26, 1997. Japan.
- OECD environment Directorate. OECD Principles of good laboratory practices, [C(97) 186/final] (1998); Environmental Health and Safety Division

Diagnosis: **Twelve rabbits** from this developmental toxicity study conducted in October 2006 have been placed in category E as the result of test article toxicity as described below.

#8867 (60 MKD), #8869 (60 MKD), #8871 (60MKD), #8874 (60 MKD), #8875 (60 MKD), #8878 (60 MKD) and #8880 (60 MKD) were found dead at the morning viability check on gestation days 19, 14, 16, 18, 14, 20 and 20, respectively. Prior clinical observations had included scant fecal output, un-groomed fur, mild to moderate body weight loss, and moderate to severely reduced feed consumption. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

#8854 (30 MKD) and #8877 (60 MKD) were euthanized per veterinary recommendation on gestation days 23 and 20, respectively, and **#8876 (60 MKD)** was euthanized at the time of abortion on gestation day 26. Prior clinical observations had included scant to zero fecal output, soft feces, un-groomed fur, red substance in cage pan, reduced level of inquisitiveness, moderate to severe body weight loss and severely reduced feed consumption. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

#7675 (60 MKD) and #8866 (60 MKD) were euthanized as scheduled on gestation day 29. Clinical signs during the course of the study included scant feces for eight days, 12-18% body weight loss over 14 or more days and severely reduced feed consumption for 10 or more days. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

Study: #9
Animals: 18 rabbits
Type of Study: Intravenous (by infusion) Dosage-Range Developmental Toxicity Study of XXX in Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Eighteen rabbits** from this dosage range-finding study conducted in August 2007-September 2007 have been place in category E due to the possibility of distress that may have been associated with the exposure to the test article.

#6199 (saline, 48 ml/kg), #2154-2155 (saline, 48 ml/kg), #2157-#2161 (300 MKD, 12 ml/kg), #2162-#2166 (600 MKD, 24 ml/kg) and #2167-#2171 (1200 MKD, 48 ml/kg) experienced purple or red discoloration (bruising) at the site of dosage administration (one or both ears) for a duration of 4 to 22 days and some also had transient swelling at the base of an ear or in the ventral neck that resulted in the inability to administer the complete dosage volume on one or more days. Feed intake in some of these animals was moderately reduced for three or more days during the dosage period with body weight losses from 0-11%. #2168 was euthanized at the end of the day on GD10 when decreased motor activity, lacrimation, ptosis, ataxia and nasal discharge were noted and failed to improve/resolve. #2171 was found dead at the morning check on GD15. #2169 was found dead at the morning check on GD18. #2167 was found dead at the morning check on GD19. #2170, the last remaining rabbit in group IV was euthanized per veterinary recommendation on GD19. All other rabbits were euthanized as scheduled at the end of the study and appeared normal at necropsy. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

Study: #10
Animals: 10 Rabbits
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study of XXX in Rabbits

Guidelines/Regulations:

- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD).
- U.S. Food and Drag Administration. Good laboratory practices for nonclinical laboratory studies, 21 C.F.R 58.
- Pharmaceutical Affairs Bureau, Ministry of Health, Labour and Welfare. GLP standard ordinance for nonclinical laboratory studies on safety of drugs, MH W Ordinance No. 21; March 26, 1997. Japan.

- OECD Environment Directorate. OECD Principles of good laboratory practices, [C(97)186/Final] (1998); Environmental Health and Safety Division.

Diagnosis: **Ten rabbits** from this developmental toxicity study conducted in November through December 2006 have been placed in category E due to tissue changes (caused by test article exposure) present at necropsy and/or clinical signs that may have resulted from some discomfort/distress from test article exposure.

#9122 (75 MKD; II), #9126 (75 MKD; II), #9160 (225 MKD; III), #9162 (750; IV), #9165 (750 MKD; IV) and **#9169 (750 MKD; IV)** were found dead with either no prior adverse clinical signs or following a few days of low feed intake, none to moderate weight loss and/or respiratory rales. Each had adverse tissue changes in the thorax at necropsy exam including one or more of the following: perinasal blood, red tracheal lining, bloody foam in the trachea, red lung lobes, spongy lung lobes, blood in the thorax, adhesions of the thymus, lungs, pericardium, diaphragm and thoracic wall, caseous masses of the lungs. The caseous masses were presumed to be a result of the test article.

#9129 (75 MKD; II), #9144 (225 MKD; III) and **#9157 (225 MKD; III)** were euthanized as scheduled on gestation day 29 and had adverse tissue changes in the thorax at necropsy exam including one or more of the following: one ore more caseous masses of the lungs, adhesions of the lungs to the thoracic walls and diaphragm and dark red lung lobes. Clinical signs for these three rabbits were either transient or mild in degree (minor to no weight loss, a few days of low feed intake) before returning to normal after the dosing period ended.

#9179 (750 MKD; IV) was euthanized by veterinary recommendation on gestation day 27 after nineteen days of weight loss (17.8% total) and low feed intake that did not respond to seventeen days of supplemental feed offerings (four types offered) or to the provision of subcutaneous fluid on the day of euthanasia. Lethargy was noted on the day prior to euthanasia.

Study: #11
Animals: 2 Rabbits
Type of Study: Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of XXX in Rabbits, Including a Toxicokinetic Evaluation

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Two rabbits** from Part B of this dosage range-finding developmental toxicity study conducted in September-October 2006 have been placed in category E as described below.

#8742 (V; 150 MKD) was euthanized on gestation day 29 as scheduled. There was a 9 % body weight loss and low feed intake since GD13. The rabbit was bright, alert and inquisitive. Although the rabbit appeared clinically normal (bright, alert and inquisitive), it is possible that some discomfort/distress from test article exposure resulted in the decreased feed intake and weight loss, therefore this rabbit was categorized as E.

#8745 (V; 150 MKD) was euthanized by veterinary request on GD25. On GD22 during routine monitoring of the study, vet staff noted a 14% body weight loss and low feed intake since GD13. Soft feces was also noted. The rabbit was bright, alert and inquisitive. Supplemental feed type and alternative water sources had been provided. At re-exam in the morning of GD24, weight loss had increased to 20% and feed intake remained low while attitude and behavior remained normal. At re-exam in the morning of GD25, decreased motor activity was noted and the rabbit was euthanized. This animal is placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

Study: #12
Animals: 53 Rabbits
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study of XXX in Rabbits, Including a Toxicokinetic Evaluation

Guidelines/Regulations:

- Guideline for Industry; detection of toxicity to reproduction for medicinal products & toxicity to male fertility, (ICH) S5(R2), last update November, 2005. Rockville (MD): U.S. Dept of Health end Human Services Food and Drug Administration.
- U.S. Food and Drug Administration. Good laboratory practices for nonclinical laboratory studies, 21 C.F.R 58.
- OECD Environment Directorate. OECD Principles of good laboratory practices, [C(97)186/Final] (1998); Environmental Health and Safety Division

Diagnosis: **Fifty three rabbits** from this developmental toxicity study conducted in December 2006 through January 2007 have been placed in category E as described below.

#74 **(V; 100 MKD)** and **#132 (II; Vehicle)** were found dead less than one hour after dosage administration. There were no adverse observations prior to death and feed consumption and weight gain were normal. Necropsy examination showed evidence of gavage error. While the duration of time between dosing and death may be short, these animals have been placed in category E acknowledging that it could be considered more than a momentary period of pain/distress.

Group II (Vehicle) rabbits #121, #123, #124, #125, #126, #127, #128, #130, #134, #135, #136, #138, #140, #57, #60, group III (10 MKD) rabbits #142, #146, #147, #148, #154, #155, #157, #61, #62, #63, #64, #65, group IV (30 MKD) rabbits #166, #167, #170, #171, #173, #174, #176, #177, #178, #179, #66, #68 and group V (100 MKD) rabbits #181, #182, #183, #185, #187, #188, #189, #191, #192, #71, #72, and #73 have been placed in category E. Each of these rabbits had zero to low feed intake (range of duration 5 to 17 days), body weight loss during pregnancy (3% to 19%), scant fecal output and un-groomed haircoat. Supportive care included the provision of second water sources, dry timothy cubes, timothy cubes moistened with water and certified fruit-flavored treats. These rabbits were either euthanized due to abortion or euthanized as scheduled at the end of the study. The majority of these rabbits were normal at necropsy examination. Gross necropsy findings were not indicative of a painful or distressful condition. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

Study: #13
Animals: 5 Rabbits
Type of Study: Oral (Stomach Tube) Dosage Range-Finding Developmental Toxicity Study of XXX in Rabbits, Including a Toxicokinetic Evaluation

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Five rabbits** at the highest dosage level (50 mg/kg/day) from Part B of this dosage range-finding developmental toxicity study conducted in November 2006 have been placed in category E as described below.

#497 (50 MKD), #9743 (50 MKD), #9758 (50 MKD), #9759 (50 MKD) and #9760 (50 MKD) had moderate to severe body weight loss (10-22% over a few days) during pregnancy and severely reduced feed intake (low to none for 4 to ten days). #9743 and #9758 were found dead, #497 and #9760 were euthanized prior to the scheduled date of euthanasia and #9759 was euthanized as scheduled. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

Study: #14
Animals: 28 rabbits
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study of XXX Rabbits, Including a Toxicokinetic Evaluation

Guidelines/Regulations:

- Guideline for Industry; detection of toxicity to reproduction for medicinal products & toxicity to male fertility, (ICH) S5(R2), last update November, 2005. Rockville (MD): U.S. Dept of Health end Human Services Food and Drug Administration.

- U.S. Food and Drug Administration. Good laboratory practices for nonclinical laboratory studies, 21 C.F.R 58.

- OECD Environment Directorate. OECD Principles of good laboratory practices, [C(97)186/Final] (1998); Environmental Health and Safety Division

Diagnosis: **Twenty eight rabbits** from this developmental toxicity study conducted in March through April 2007 have been placed in category E as described below.

#1196 (V; 30 MKD) was found dead on GD11 one hour after dosage administration. There were no adverse observations prior to being found dead and feed consumption and weight gain were normal. Necropsy exam revealed that the cause of death was a result of a gavage error. While the duration of time between dosing and death may be short, this animal has been placed in category E acknowledging that it could be considered more than a momentary period of pain/distress.

#1216 (I; 0 MKD) and #1290 (V; 30 MKD) had a decrease in activity level, 10 to 14 days of low feed intake and 13-18% body weight loss. #1216 was found dead at the morning viability check. #1290 was euthanized by veterinary recommendation. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

#1182 (II; 0.2 MKD), #840 (II;0.2 MKD), #1230 (II; 0.2 MKD0, #1248 (III; 3 MKD) #1192 (IV;10 MKD), #1261 (IV; 10 MKD), #1264 (IV; 10 MKD), #1268 (IV; 10 MKD), #1269 (IV;10 MKD), #1198 (V; 30 MKD), #1282 (V; 30 MKD), #1286 (V; 30 MKD), #1288 (V; 30 MKD), #1292 (V; 30 MKD), #1294 (V; 30 MKD), #1297 (V; 30 MKD) and #1300 (V; 30 MKD.) These rabbits had low feed intake for 4 to 16 days. The body weight loss in these rabbits was low to severe (3-28%.) These animals were either found dead (1 rabbit), euthanized at the time of abortion (4 rabbits), euthanized when dosage group V was terminated (5 rabbits), euthanized by veterinary recommendation (1 rabbit) or euthanized as scheduled at the end of the study (6 rabbits.) These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

#1281 (V:30 MKD), #1283 (V; 30 MKD), #1285 (V;30 MKD), #1291 (V;30 MKD), #1293 (V;30 MKD), #1296 (V;30 MKD), #1298 (V;30 MKD) and #1299 (V;30 MKD.) The body weight loss in these rabbits was none to low (0-9%), the behavior and attitude were normal and feed intake levels were moderate to good in all rabbits except one which had fair intake levels. These animals were either euthanized at the time of abortion (3 rabbits) or euthanized when dosage group V was terminated (5 rabbits.) While the clinical signs and/or necropsy findings are not suggestive of an animal that experienced pain or distress, these rabbits have been placed in E, conservatively, because they were part of the high dose group (described immediately above) that was terminated early.

Study: #15
Animals: 2 Rabbits
Type of Study: Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of XXX in Rabbits, Including a Toxicokinetic Evaluation

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Two rabbits** from Part A of this dosage range-finding developmental toxicity study conducted in September 2007 have been placed in category E as described below.

#1999 (100 MKD) lost body weight daily (6.3% cumulative loss) and feed intake was moderately to severely reduced during the five day study. Hypereactivity was noted at the 2 hour check on study day 2. This rabbit was euthanized as scheduled at the end of the study and appeared normal at necropsy exam. This animal is placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

#2000 (200 MKD) was noted to have tremors, head tilt, prostration, hyperreactivity, loss of righting reflex and respiratory difficulty 1 hour after dosing on study day 1. Euthanasia was recommended by the veterinary staff, however the rabbit died en route to the necropsy lab. Necropsy results were consistent with a gavage error. While action was taken immediately upon recognition of the clinical signs, this rabbit has been placed in E acknowledging that the precise duration of the signs may have been more than momentary.

Study: #16
Animals: 2 Rabbits
Type of Study: Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of XXX in Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Two rabbits** from this dosage range developmental toxicity study conducted in September 2007-October 2007 have been placed in category E as described below.

#8899 (Satellite, 500 MKD) lost body weight daily beginning on the first day of dosage until scheduled euthanasia for a cumulative loss of 10%. Feed intake was reduced to a moderate level from GD8 to GD14 and then reduced to a low level from GD14 to GD19. Reduced fecal output was observed on GD15 and discolored urine was observed on GD15 and GD16. At exams, this rabbit remained bright, alert and active until the day of scheduled euthanasia when a reduction in the level of inquisitiveness was noted. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

#2471 (Main, 500 MKD) lost 7.3% body weight from GD14 to GD18. Feed was reduced daily beginning on GD14 from a good level to a fair level on GD18. This rabbit aborted and was euthanized on GD19. This animal is placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

Study: #17
Animals: 7 Rabbits
Type of Study: Intravenous and Oral Dosage-Range Developmental Toxicity Study of XXX in Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Seven rabbits** from this dosage range-finding developmental toxicity study conducted in March through April 2007 have been placed in category E as described below.

#858 (5 MKD Intravenous), #880 (10 MKD Gavage), #881 (30 MKD Gavage),
#882 (30 MKD Gavage) and #886 (60 MKD Gavage) experienced minor, transient body weight loss (1.6%-10.3% over 1 to 5 days) and a transient reduction in feed intake (low intake for 1 to 5 days.) #882 was found dead on gestation day 9 prior to daily dosage. #858, #880, #881 and #886 had no adverse signs except scant fecal output (1 to 5 days duration), were euthanized as scheduled at the end of the study. These animals are placed in category E due to the possibility of

distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

#889 (60 MKD Gavage) and #890 (60 MKD Gavage) experienced 21% and 16 %, weight loss, respectively, over 16 to 20 days. Feed intake was also low during this period. #889 consumed the provided timothy cubes and #890 gained 2% weight when feed intake steadily improved at the end of gestation. Scant fecal output was the only clinical sign in these rabbits. The animals were bright, alert and inquisitive at all exams. #889 aborted and was euthanized. #890 was euthanized as scheduled at the end of the study. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

Study: #18
Animals: 18 Rabbits
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study of XXX in Rabbits

Guidelines/Regulations:

- Guideline for Industry; detection of toxicity to reproduction for medicinal products & toxicity to male fertility, (ICH) S5(R2), last update November, 2005. Rockville (MD): U.S. Dept of Health end Human Services Food and Drug Administration.

- U.S. Food and Drug Administration. Good laboratory practices for nonclinical laboratory studies, 21 C.F.R 58.

- OECD Environment Directorate. OECD Principles of good laboratory practices, [C(97)186/Final] (1998); Environmental Health and Safety Division

Diagnosis: **Eighteen rabbits** from this developmental toxicity study conducted in May 2007-June 2007 have been placed in category E as described below.

#1808 (vehicle), #1811 (vehicle), #1846 (3 MKD), #1849 (3 MKD), #1852 (10 MKD), #1867 (10 MKD), #1387 (30 MKD), #1877 (30 MKD), #1883 (30 MKD), #1888 (30 MKD), #1891 (30 MKD), #1892 (30 MKD), #1893 (30 MKD), #1896 (30 MKD) and #1898 (30 MKD) experienced mild body weight loss (3-10%) and moderate to severe reduction in feed consumption (3-7 days duration) during the dosage period. The only clinical sign was reduced fecal output. These rabbits were euthanized as scheduled at the end of the study and were normal at necropsy examination. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

#1887 (30 MKD), #1894 (30 MKD) and #1900 (30 MKD) experienced moderate to severe body weight loss (15-19%) and severely reduced feed intake during dosage administration. Clinical signs observed in #1887 and #1894 included reduced fecal output and un-groomed fur. #1900 also had lethargy and dehydration. #1887 and #1900 were euthanized as scheduled at the end of the study. #1894 was found dead at the morning viability check on gestation day 27. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

Study: #19
Animals: 3 Rabbits
Type of Study: Intravenous Dosage-Range Developmental Toxicity Study of XXX in Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Three rabbits** from this dosage range-finding developmental toxicity study conducted in September-October 2006 have been placed into category E as described below.

Rabbit # 8189 (III; 20 MKD) was found dead in the morning of GD29. The rabbit was normal on necropsy examination. The rabbit had a 16% body weight loss between GD16 and GD28 and two days of fair-to-low feed intake. The rabbit was bright, alert, inquisitive and well groomed. This animal is placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

Rabbit #8190 (III: 20 MKD) was found dead in the morning of GD29. The rabbit's heart, kidneys and liver were pale at necropsy examination. This rabbit was examined by request on GD24 for 4% body weight lost over the previous four days. Feed intake was low for three days. The rabbit was bright, alert, and inquisitive. A timothy cube was provided daily as an alternative food source. At re-exam on GD26, the timothy cube was being eaten, behavior remained normal and an additional 2.9% weight had been lost. At re-exam on GD28 (the day before scheduled euthanasia), no additional body weight was lost and behavior remained normal. This animal is placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

Rabbit #8197 (IV; 40 MKD) was euthanized on GD27 following abortion. The rabbit's heart, kidneys and liver were pale at necropsy examination. This rabbit had a 12% body weight loss between GD11-GD24 and 8 days of fair-low feed intake. The rabbit was bright, alert and inquisitive. A timothy cube was provided as an alternative food source. At re-exam on GD26, an additional 2% body weight was lost, feed intake remained low and the timothy cubes were uneaten. The rabbit remained bright, alert and inquisitive. A timothy cube moistened with water was provided to help stimulate interest in eating. At re-exam in the morning on GD27, and additional 1.7% body weight was lost, feed intake was low and the rabbit remained bright, alert and inquisitive. This animal is placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

Study: #20
Animals: 95 Rabbits
Type of Study: Intravenous Developmental Toxicity Study of XXX in Rabbits

Guidelines/Regulations:

- Guideline for Industry; detection of toxicity to reproduction for medicinal products & toxicity to male fertility, (ICH) S5(R2), last update November, 2005. Rockville (MD): U.S. Dept of Health end Human Services Food and Drug Administration.
- U.S. Food and Drug Administration. Good laboratory practices for nonclinical laboratory studies, 21 C.F.R 58.
- OECD Environment Directorate. OECD Principles of good laboratory practices, [C(97)186/Final] (1998); Environmental Health and Safety Division

Diagnosis: **Ninety five rabbits** from this developmental toxicity study conducted in February 2007-March 2007 have been placed in category E as described below.

#588 (I; Control), #589 (I; Control), #591 (I; Control) and #600 (I; Control) experienced bruising (purple discoloration) at the site of dosage administration of one or both ears for a duration of 5 to 10 days. #589 also experienced severely reduced feed intake for 3 days, 9% body weight loss and scant fecal output. These rabbits were euthanized as scheduled at the end of the study and appeared normal at necropsy examination. These rabbits were conservatively placed in category E due to the possibility that the bruising may have been associated with some minor level of discomfort/distress even though the rabbits appeared clinically normal otherwise. In addition, #589 is placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

#601-#604 (II; Control), #606-#607 (II; Control), #609-#617 (II; Control), #619-#622 (II; Control), #624 (II; Control), #8794 (II; Control), #628-#634 (III; 10MKD), #636-#651 (III; 10 MKD), #653-#655 (IV; 20 MKD), #657-#675 (IV;20 MKD) and #676-#700 (V; 40 MKD) experienced bruising (purple discoloration) at the site of dosage administration of one or both ears for a duration of 4 to 10 days and/or moderately to severely reduced feed consumption for 5 to 18 days. These rabbits were euthanized as scheduled at the end of the study with the exception of #682 and #692. These two rabbits were euthanized at the time of abortion, appeared normal at necropsy exam and all fetuses were dead. These rabbits were conservatively placed in category E due to the possibility that the bruising may have been associated with some minor level of discomfort/distress even though the rabbits appeared clinically normal otherwise. In addition, these animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake.

Study: #21
Animals: 27 Rabbits
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study in New Zealand While Rabbit

Guidelines/Regulations:

- U.S. Dept of Health and Human Services Food end Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD).
- U.S. Food and Drug Administration. Good laboratory practices for nonclinical laboratory studies, 21 C.F.R. 58.
- Pharmaceutical Affairs Bureau, Ministry of Health, Labour end Welfare. GLP standard ordinance for nonclinical laboratory studies on safety of drugs, MHW Ordinance No. 21; March 26, 1997. Japan.
- OECD Environment Directorate. OECD Principles of good laboratory practices, [C(97)186/Fiml] (1998); Environmental Health and Safely Division.

Diagnosis: **Twenty seven rabbits** from this developmental toxicity study conducted in November- December 2006 have been placed in category E for the reasons described below.

#8560, #8562, #9461, #9463, #9465, #9466, #9471, #9473, #9474, #9479, #9480, #9482, #9483, #9485, #9486, #9487, #9488, #9489, #9490, #9492, #9493, #9494, #9496, #9497, #9499, #8563 and #8565. These rabbits had necropsy findings of hemorrhage in one or more organs, and/or acute body weight loss (range 4% to 28% over 4 to 21 days) and/or the low feed intake (over 2 to 14 days) . These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss or because of the necropsy findings.

Study: #22
Animals: 36 Guinea Pigs
Type of Study: Effect of Operating Room Light (ORL) Exposure Dose, ORL Filtration and Time Dependence Between Administration and ORL Exposure on Phototoxicity Induced by a Single Intramuscular XXX Administration in Neonatal Albino Hairless Guinea Pigs

Guidelines/Regulations:

- U.S. U.S. Dept of Health end Human Services Food and Drug Adminstration, (CDER). Guidance for Industry: photosafety testing; May 2003. Rockville (MD).
- U.S. Food and Doug Administration. Good laboratory practices for nonclinical laboratory studies, 21 CF.R. 58.

Diagnosis: **Thirty six guinea pigs** from this study have been placed in category E as described below.

#22617, #22696, #22629, #22644, #22661 and **#22697** were euthanized as scheduled and experienced 1-3 days of dehydration with or without acute body weight loss (range of 0-17%.)

#22626, #22698, #22725, #22686, #22687, #22694, #22703 and **#22716** were euthanized due to clinical signs of weakness, decreased activity, dehydration and acute weight loss (range of 3-19%.)

#22610, #22618, #22620, #22656, #22664, #22672, #22678, #22700, #22704, #22706, #22713, #22732, #22613, #22622, #22623, #22624, #22651, #22653, #22675, #22689, #22702 and **#22729** were found dead primarily at morning viability checks. Eleven animals had no clinical signs prior to death. The remaining animals experienced 1-3 days of dehydration and acute body weight loss (range of 7-22%) from the day of dosage to the time of death. #22610 was assigned to the saline control group and was normal at necropsy exam. This animal's death was determined to be related to its relatively small size at assignment to study/birth.

All 36 animals were conservatively assigned to category E as it is possible that some discomfort/distress may have been associated with either the dehydration and/or weight loss.

Study: #23
Animals: 16 Rabbits
Type of Study: Percuteneous Developmental Toxicity Study of XXX in Rabbits

Guidelines/Regulations:

- Guideline for Industry; detection of toxicity to reproduction for medicinal products & toxicity to male fertility, (ICH) S5(R2), last update November, 2005. Rockville (MD): U.S. Dept of Health end Human Services Food and Drug Administration.

- U.S. Food and Drug Administration. Good laboratory practices for nonclinical laboratory studies, 21 C.F.R 58.
- OECD Environment Directorate. OECD Principles of good laboratory practices, [C(97)186/Final] (1998); Environmental Health and Safety Division

Diagnosis: **Sixteen rabbits** from this developmental toxicity study conducted in June 2007-July 2007 have been placed in category E as described below.

#2513 (vehicle), #2514 (acclimated, replaced prior to dosage), #2520 (vehicle), #2523 (placebo), #2534 (placebo), #2535 (placebo), #2538 (placebo), #2542 (100 ng/kg/day), #2543 (100 ng/kg/day), #2552 (100 ng/kg/day), #2555 (100 ng/kg/day), #2557 (100 ng/kg/day), #2566 (400 ng/kg/day), #2568 (400 ng/kg/day), #2569 (400 ng/kg/day) and #2574 (400 ng/kg/day) experienced mild to severe body weight loss (7-27% over 4 to 18 days) and moderate to severe reduction in feed consumption during the acclimation and/or dosage period. Thirteen of these rabbits regained body weight beginning after the first several days of dosage or after the dosage period ended. #2534 was euthanized at the time of abortion on gestation day 19. #2574 was euthanized per the recommendation of a veterinarian on gestation day 22 when a decline in attitude and less active behavior first occurred. #2514 was found dead and appeared normal at necropsy exam. All other rabbits were euthanized as scheduled at the end of the study. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss or because of the necropsy findings.

Study: #24
Animals: 8 Rabbits
Type of Study: Dose-Range Developmental Toxicity Study of Subcutaneously Administered in Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Eight rabbits** from this dosage range-finding study conducted in August 2007-September 2007 have been placed in category E as described below.

#1579-1581 (20 mg/kg), #1582 and #1584 (25 mg/kg) and #1585-1587 (30 mg/kg) were euthanized as scheduled on study day 14. These rabbits had clinical signs observed at one or more dosage sites. These included black discoloration and/or scab(s) and/ulceration(s). The duration from time of onset until scheduled euthanasia was two to ten days. In some animals, the feed intake was moderately reduced for a period ranging from one day to several days. Although none of the rabbits showed signs of reaction to manipulation of the injection sites, the dermal observations combined with the moderately reduced feed intake may have been indicative that these animals experienced some level of discomfort/distress and therefore, were conservatively categorized as E.

Study: #25
Animals: 13 Rabbits
Type of Study: Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of XXX in Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Thirteen rabbits** from this dosage range-finding developmental toxicity study conducted in June 2007-July 2007 have been placed in category E as described below.

#1332 (3 MKD), #1337 (30 MKD) and #1339 (30 MKD) experienced mild body weight loss (6-7%) and moderate reduction in feed consumption during the dosage period. Clinical signs included reduced fecal output and/or soft feces. These rabbits were euthanized as scheduled at the end of the study and were normal at necropsy examination. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss or because of the necropsy findings.

#1341 - #1349 (100 MKD and 300 MKD groups) experienced clinical signs of ptosis, lethargy and tachypnea on four or more days of dosage. In addition, six of these rabbits had minor weight loss (0-5%) and 3 had moderate to severe weight loss (10-22%). Feed consumption varied from no effect to severely reduced. **#1350(300 MKD)** was found dead 26 minutes after dosing on the first day. No clinical signs were noted prior to death. With the exception of #1350, these rabbits are placed in category E due to the possibility that some of the clinical signs may have been consistent with experiencing some level of discomfort/distress. #1350 was included, conservatively, since all other rabbits in the same dose group were categorized as E.

Study: #26
Animals: 8 Rabbits
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study of XXX in Rabbits. Including a Toxicokinetic Evaluation

Guidelines/Regulations:

- Guideline for Industry; detection of toxicity to reproduction for medicinal products & toxicity to male fertility, (ICH) S5(R2), last update November, 2005. Rockville (MD): U.S. Dept of Health end Human Services Food and Drug Administration.
- U.S. Food and Drug Administration. Good laboratory practices for nonclinical laboratory studies, 21 C.F.R 58.
- OECD Environment Directorate. OECD Principles of good laboratory practices, [C(97)186/Final] (1998); Environmental Health and Safety Division

Diagnosis: **Eight rabbits** from the main portion of this developmental toxicity conducted in September 2007 through October 2007 have been placed in category E as described below.

#3211 (vehicle), #3219 (vehicle), #3229 (3 MKD), #3258 (10 MKD), #3261 (30 MKD), #3262 (30 MKD), #3265 (30 MKD) and #3273 (30 MKD) experienced moderate to severe reduction in feed consumption for 3 to 7 days during the dosage period and body weight loss of 3-8%. Clinical signs included reduced fecal output and un-groomed coat. These rabbits were euthanized as scheduled at the end of the study and appeared normal at necropsy examination. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

Study: #27
Animals: 31 Rabbits
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study of XXX in Rabbits

Guidelines/Regulations:

- Guideline for Industry; detection of toxicity to reproduction for medicinal products & toxicity to male fertility, (ICH) S5(R2), last update November, 2005. Rockville (MD): U.S. Dept of Health end Human Services Food and Drug Administration.
- U.S. Food and Drug Administration. Good laboratory practices for nonclinical laboratory studies, 21 C.F.R 58.
- OECD Environment Directorate. OECD Principles of good laboratory practices, [C(97)186/Final] (1998); Environmental Health and Safety Division

Diagnosis: **Thirty one rabbits** from this developmental toxicity study conducted in July 2007 have been placed in category E as described below.

Many of these animals (**twenty seven rabbits**) experienced mild to moderate body weight loss and moderate to severe reduction in feed consumption during the dosage period. Clinical signs included reduced fecal output. These rabbits were euthanized as scheduled at the end of the study and were normal at necropsy examination. **Four** rabbits experienced moderate to severe body weight loss and severe reduction in feed consumption during the dosage period and were euthanized at the time of abortion. The animals were normal at necropsy examination. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss or because of the necropsy findings.

Study: #28
Animals: 17 Rabbits
Type of Study: A Pilot Embryo-Fetal Development and Toxicokinetic Study of XXX Administered Orally (Gavage) in New Zealand White Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Seventeen rabbits** from this dosage range-finding developmental toxicity study conducted in July 2007 have been placed in category E as described above.

#2401 (100 MKD), #2402 (100 MKD), #2403 (100 MKD), #2405 (100 MKD) and #2427 (100 MKD) experienced mild to moderate body weight loss and moderate reduction in feed consumption during the dosage period. Clinical signs included reduced fecal output. These rabbits were euthanized as scheduled at the end of the study and were normal at necropsy examination. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss or because of the necropsy findings.

#2406 (300 MKD), #2407 (300 MKD), #2408 (300 MKD), #2409 (300 MKD), #2410 (300 MKD) and #2428 (300 MKD) experienced moderate to severe body weight loss and severely reduced feed intake beginning at the start of dosage administration. Clinical signs included reduced fecal output, soft feces and un-groomed fur. #2407 was found dead after dosage on gestation day 11. #2406, #2408, #2409, #2410 and #2428 were euthanized on gestation day 12 when this dosage level was terminated. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss or because of the necropsy findings.

#2416 (750 MKD), #1538 (750 MKD), #2418 (750 MKD), #2419 (750 MKD), #2420 (750 MKD) and #2429 (750 MKD) experienced moderate body weight loss and severely reduced feed intake beginning at the start of dosage administration. Clinical signs included reduced fecal output, soft feces, un-groomed fur, ptosis and excess salivation. #2416, #2419 and #2420 were found dead after dosage administration on gestations days 10, 10 and 11 respectively. #2429 died while being transported to the necropsy lab for euthanasia for moribund condition. #1538 and #2418 were euthanized on gestation day 11 when this dosage level was terminated. These animals (except for #2429) are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss or because of the necropsy findings.

Study: #29
Animals: 33 Rabbits
Type of Study: An Embryo-Fetal Development and Toxicokinetic Study of XXX Administered Orally (Gavage) in New Zealand White Rabbits

Guidelines/Regulations:

- Guideline for Industry; detection of toxicity to reproduction for medicinal products & toxicity to male fertility, (ICH) S5(R2), last update November, 2005. Rockville (MD): U.S. Dept of Health end Human Services Food and Drug Administration.

- U.S. Food and Drug Administration. Good laboratory practices for nonclinical laboratory studies, 21 C.F.R 58.

- OECD Environment Directorate. OECD Principles of good laboratory practices, [C(97)186/Final] (1998); Environmental Health and Safety Division

Diagnosis: **Thirty three** rabbits from this developmental toxicity study conducted in September 2007 have been placed in category E as described below.

#2864 (vehicle; 0 MKD) and #2870 (vehicle; 0 MKD) experienced 2 days of reduced feed intake with corresponding body weight loss (3-4%) in association with the clinical observation of rales over a 3 to 4 day period of the dosage period. These rabbits were euthanized as scheduled at the end of the study and appeared normal at necropsy exam. These rabbits are being conservatively categorized as E due to the possibility that some level of discomfort/distress was associated with rales.

#2805 (10 MKD), #2820 (10 MKD), #2827-#2828 (30 MKD), #2836 (30 MKD), #2839 (30 MKD), #2889 (30 MKD), #2891-2892 (30 MKD), #2841-2842 (125 MKD), #2844-2845 (125 MKD), #2847-2860 (125 MKD), #2893-2896 (125 MKD) experienced 5 to 13 days of moderately to severely reduced feed intake with corresponding body weight loss (4-26%) in association with reduced fecal output during the dosage period. There was daily body weight gain after the dosage period ended. All rabbits were euthanized as scheduled at the end of study and all appeared normal at necropsy. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss or because of the necropsy findings.

Study: #30
Animals: 14 Rabbits
Type of Study: A Pilot Embryo-Fetal Development and Toxicokinetic Study of XXX Administered Orally (Gavage) in New Zealand White Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Fourteen rabbits** from this dosage range-finding developmental toxicity study conducted in August 2007-September 2007 have been placed in category E as described below.

#3018-3020 (100 MKD), #3011-3013 (300 MKD), #3015 (300 MKD), #3028 (300 MKD), #3021-3025 (600 MKD) and #3029 (600 MKD) experienced mild to moderate body weight loss (4-12%) and moderate to severe reduction in feed consumption during the dosage period. Clinical signs included reduced fecal output, mucoid feces, un-groomed coat and decreased activity. #3022 (600 MKD) was found dead after dosage on GD9. #3025 (600 MKD) was found dead at the morning check on GD10. #3021 (600 MKD) died on GD10 en route to necropsy before euthanasia could be performed after dosage. The last 2 rabbits in this group (#3023 and #3029) were found dead at the morning check on GD11. #3013 (300 MKD) was euthanized by veterinary recommendation on GD12. #3011 (300 MKD) was found dead at the morning check on GD13. The remaining four animals in this group (#3012, #3014, #3015, and #3028) were euthanized on GD13 when this dosage level was terminated. #3019 (100 MKD) was found dead at the morning check on GD13. #3018 (100 MKD) and #3020 (100 MKD) were euthanized as scheduled at the end of the study. These animals are placed in category E due to either them being found dead with a history of clinical signs prior to death and/or the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss or because of the necropsy findings.

Study: #31
Animals: 9 Rabbits
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study of XXX in Rabbits

Guidelines/Regulations:

- The requirements of the U.S. Environmental Protection Agency (EPA) , the Ministry of Agriculture, Forestry and Fisheries and the Organisation for Economic Cooperation end Development will be used as the basis for study design.

Diagnosis: **Nine rabbits** from this developmental toxicity study conducted in July 2007-August 2007 have been placed in category E as described below.

#2616 (I) and #2705 (V) were found dead at the end of day post dosage checks on gestation day 25 and 20, respectively. Body weight losses were 18% and 11 % respectively. Feed intake was severely reduced in both animals. #2616 had scant fecal output but was otherwise normal in appearance and attitude/behavior. #2705 experienced rales on two occasions several days prior to death. Necropsy results on both animals were consistent with gavage error.

#2646 (II) was found dead at the 1-2 hour post dosage check on gestation day 7. While on study, there was no body weight loss, no reduction in feed consumption and no clinical signs prior to death. Necropsy results were consistent with gavage error.

#2625 (II), #2651 (III), #2697 (V), #2698 (V) and #2699(V) experienced mild to moderate body weight loss (9-14% over 2 to 23 days) and moderate to severe reduction in feed consumption during the dosage period. Clinical signs included reduced fecal output. #2698 and #2699 were euthanized as scheduled at the end of the study and were normal at necropsy. #2651 was found dead at the end of day post dosage check on gestation day 27. Stomach erosions were present at necropsy exam. #2697 was euthanized per veterinary recommendation due to moribund condition on gestation day 13. At necropsy exam, all lung lobes were dark red and stomach erosions were present. These animals (except for #2697 – moribund euthanasia) are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss or because of the necropsy findings. **#2701 (V)** experienced tachypnea on five occasions after daily dosage and ataxia on one occasion after daily dosage prior to scheduled euthanasia at the end of the study. There was no body weight loss and no feed reduction. This rabbit was normal at necropsy examination. This rabbit was conservatively categorized as an E as there may have been some level of discomfort/distress associated with the episodes of tachypnea and/or ataxia.

Study: #32
Animals: 2 Rabbits
Type of Study: Intravenous Study of Embryo-Fetal Development in Rabbits

Guidelines/Regulations:

- U.S. Dept of Health and Human Services Food end Drug Administration on Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD).
- U.S. Food and Drug Administration Good Laboratory practices for nonclinical laboratory studies, 21 C.F.R. 58; lest revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: **Two rabbits** from this intravenous embryo-fetal developmental toxicity study conducted in October-November 2006 have been placed in category E as described below.

#9244 (II; 10 MKD) and #9288 (IV; 100 MKD) had a scab present on one ear a few days after daily dosage began. A scab 4.0 x 1.0 cm was present on the right ear of #9244 on gestation days 11 through 18. Feed intake was good during this time and there was no weight loss. A scab 3.5 x 0.5 cm was present on the left ear of #9288 on gestation days 11 through 21. Feed intake was good during this time and there was no weight loss. Both rabbits were euthanized as scheduled on gestation day 29. These rabbits have been conservatively placed in category E because the scabs were located at the site of test article injection and the inflammatory process resulting in formation of scabs of this size may have been associated with some level of discomfort/distress.

Study: #33
Animals: 1 Rabbit
Type of Study: Thirteen-Day Oral Range-Finding Study in Pregnant Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **One rabbit** from Part B of this dosage range-finding study conducted in December 2006 has been placed in category E as described below.

#21 (20 MKD) was dosed once daily by stomach tube from gestation day 7 through19 and euthanized in moribund condition on gestation day 20. Clinical signs recorded the day before euthanasia were red colored urine, un-groomed coat and soft/scant feces. The rabbit was examined daily from gestation day 17 through 20 and two water sources and a timothy cube were provided daily. On gestation days 17 and 18, no pain/distress was diagnosed because BW loss was minimal, feed intake was moderate and behavior and attitude were normal. On gestation day 19 distress was diagnosed when BW loss was 12%, mucous membranes were yellow and behavior was subdued. Re-examination was done right away the next morning (gestation day 20) at which time the rabbit was euthanized for decreased activity, prostrate posture, coldness and yellow mucous membranes. BW loss from gestation day 7 to 20 was 18% and feed intake was low from gestation day 18 through 20. Necropsy exam findings included liver necrosis and icterus. This rabbit has been placed in category E because distress was diagnosed on the day prior to progression to moribund condition and euthanasia.

Study: #34
Animals: 11 Rabbits
Type of Study: Thirteen-Day Oral Range-Finding Study in Pregnant Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Eleven rabbits** from this dosage range-finding study conducted in May-June 2007 have been placed in category E as described below.

#1726 (180 MKD), #1727 (180 MKD) and #1703 (180 MKD) were found dead one hour after the first dosage on GD7. No adverse signs were observed prior to death. Necropsy exam showed white areas on the hearts, dark red livers and mottled lungs. **#1719 (120 MKD), #1720 (120 MKD), #1721 (120 MKD), #1723 (120 MKD), #1724 (120 MKD), #1725 (90 MKD), #1728 (90 MKD) and #1729 (90 MKD)** experienced transient clinical signs following dosage on one or more days. These signs included ataxia, loss of righting reflex and decreased activity and in all instances the animals appeared normal at the time of each daily dosage. Weight loss was none to minor (0-6% over a 1 to 10 day period) except for #1720 with a loss of 16% over the dosage period which was partially regained in the post dosage period. Feed intake was good except for #1720 with low intake during the dosage period. #1719 and #1723 were found dead on GD19 and GD14 respectively. #1728 was euthanized on GD19 due to clinical signs. #1720, #1721, #1724, #1725 and #1729 were euthanized as scheduled at the end of the study and were normal at necropsy. These animals were categorized as E either due to being found dead (and in dosing groups with prior clinical signs), necropsy findings and/or the possibility that some level of discomfort/distress was associated with the transient clinical signs.

Study: #35
Animals: 9 Rabbits
Type of Study: Dosage-Range Developmental Toxicity Study of following Oral (Stomach Tube) Administration in Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Nine rabbits** from this dosage range-finding developmental toxicity study conducted in August 2007- September 2007 have been placed in category E as described below.

#1542 (vehicle) experienced severely reduced feed intake and 6% body weight loss over the first three days of dosage. Scant fecal output was the only clinical sign. This rabbit was euthanized as scheduled on day 6 of the study. This animal is placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

#1543 (0.75 MKD), #1544 (0.75 MKD), #1545 (1.0 MKD), #1546 (1.0 MKD), #1547 (1.5 MKD), #1548 (1.5 MKD), #1549 (2.0 MKD) and #1550 (2.0 MKD) experienced acute body weight loss (4 -8% loss daily totaling 8-25%) and consumed no feed or feed supplements during the study. #1549 and #1550 were found dead at the morning viability check on study day 2. No clinical signs were present on study day 1. Necropsy of these animals showed urinary bladders full of red fluid. #1548 was euthanized per veterinary recommendation at the end of study day 2 because there was progression to moribund condition. Clinical signs that were present for most of the day included decreased activity, ataxia, salivation, dypsnea, clear nasal discharge and rales. No adverse observations were noted at necropsy exam. #1545, #1546 and #1547 were euthanized on study day 4. Clinical signs included scant fecal output, decreased activity, ataxia, dypsnea, cold to touch, vocalization and mydriasis. No adverse observations were noted at necropsy exam. Clinical signs, in addition to the body weight loss and decreased feed consumption, in the rabbits that survived until scheduled euthanasia (#1543, #1544) included scant fecal output and urine-stained fur.

Study: #36
Animals: 7 Rabbits
Type of Study: Percutaneous Dosage-Range Developmental Toxicity Study of Topical Gel in Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Seven** rabbits from this dosage range-finding study conducted in December 2006 have been place in category E as described below.

#9781 (II;1.75 MKD), #9782 (II;1.75 MKD), #9790 (IV; 7 MKD), #9792 (IV;7 MKD), #9799 (V;12 MKD), #8712 (III;3.5 MKD) and **#8718 (V;12 MKD)** had moderate to severe body weight loss (13 to 25%) and severe to moderately severe reduction in feed intake during the 13 day dosage period. Body weight loss was entirely or partially re-gained in the post dosage period. Other clinical signs included scant fecal output and grade 2 or 3 skin grade observations (erythema, edema and/or flaking.) None of the dosage sites were sensitive to the touch. Attitude and behavior remained normal. Each of these rabbits was euthanized as scheduled at the end of the study. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

Study: #37
Animals: 1 Rabbit
Type of Study: Percutaneous Repeated Dose 14-Day Tolerance Study of Topical Gel in Female
Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **One rabbit** from this dermal 14-day tolerance study conducted in November 2006 has been placed in category E

as described below. Part of the study design included the use of Elizabethan collars and jackets to prevent the rabbits from ingesting the topically applied teat article.
#7944 (II; 7 MKD) was examined at 8:44 am on study day 7 when found to have the slipped its lower jaw under the Elizabethan collar. There was a small abrasion (0.4 x 0.1 cm) at one corner of the mouth, evidence of excess salivation and the rabbit was otherwise bright, alert, active and inquisitive. During the next few days, feed consumption was slightly decreased and the rabbit lost approximately 3 – 4 % of its body weight, although it continued to be bright, alert and inquisitive. The mucosa at the corners of the mouth was noted to be slightly swollen. At re-exam on study day 12, feed intake improved and the rabbit was observed playing with toys during the exam. Body weight was gained daily and feed intake remained at a moderate to good level until scheduled euthanasia on study day 15. This rabbit has been placed in category E because it is presumed that the accident with the Elizabethan collar resulting in slight abrasion, mucosal swelling was associated with some level of discomfort/distress as indicated by several days of decreased feed consumption and subsequent body weight loss.

Study: #38
Animals: 3 Rabbits
Type of Study: Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of XXX in Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Three** rabbits from this dosage range-finding study conducted in May 2007 have bee placed in category E as described below.

#1752 (vehicle) lost 10% body weight from GD 20 to 23 and had low feed intake during this same time. No other clinical signs were present and the rabbit was euthanized on GD23 due to abortion. The rabbit was otherwise normal at necropsy examination. This rabbit has been placed in category E due to fetal death and abortion that may have been related to the vehicle and/or distress from dosage administration or other study procedures.

#1772 (45 MKD) lost 6.5% body weight from GD13 to 19 and feed intake was reduced to a fair level during this same time. No other adverse clinical signs were present. The rabbit gained body weight daily following the end of the dosage period when feed intake improved to 100%. The rabbit was euthanized as scheduled at the end of the study. This animal is placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

#1782 (45 MKD Satellite) lost 8.8% body weight from GD14 to 20 and feed intake was low from GD16 to 18 and on GD20. No other clinical signs were present. This satellite rabbit was euthanized as scheduled on GD20. This animal is placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

Study: #39
Animals: 5 Rabbits
Type of Study: Developmental Toxicity Study of XXX When Administered by Intravenous Injection to Pregnant Rabbits

Guidelines/Regulations:

- U.S. Dept of Health and Human Services Food end Drug Administration on Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD).
- U.S. Food and Drug Administration Good Laboratory practices for nonclinical laboratory studies, 21 C.F.R. 58; lest revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: **Five rabbits** from this developmental toxicity study conducted in April through May 2007 have been placed in category E as described below.

#5869 (vehicle) had a scab (1.0 x 0.5 cm) present on the right ear from GD12-GD25. No pain or discomfort to handling of the ear was present and no other clinical signs were present. This rabbit gained body weight daily, had good feed intake levels every day and was euthanized as scheduled at the end of the study. Necropsy examination was normal. This rabbit has been placed in category E conservatively acknowledging that dosage and/or blood collection procedures involving the ear may have resulted in the scab and because a scab of this size may have been associated with some level of discomfort/distress at some point in development.

#1419 (vehicle), #1437 (10 mg/kg), #1464 (100 mg/kg) and #1476 (100 mg/kg) experienced minor BW loss (5 to 8%) over five to nine days and had low feed intake over four to seven days. Other clinical signs present ranged from none (#1419) to scant fecal output (#1437, ##1464) and un-groomed coat (#1476.) # 1419 and # 1476 regained all of the lost body weight when the dosage period ended. #1419, #1437 and #1476 were euthanized as scheduled at the end of the study and necropsy examination was normal. #1464 was found dead at the morning viability check on GD28. Necropsy examination was normal. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

Study: #40
Animals: 26 Rabbits
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study of in Rabbits

Guidelines/Regulations:

- U.S. Dept of Health and Human Services Food end Drug Administration on Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD).
- U.S. Food and Drug Administration Good Laboratory practices for nonclinical laboratory studies, 21 C.F.R. 58; lest revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: **Twenty six** rabbits from this developmental toxicity study conducted in June 2007 have been placed in category E as described below.

#1611 (I; 0 MKD) was euthanized at the time of abortion on GD28. This rabbit lost 15.5% body weight over 16 days and had low feed intake during this same period. The only clinical observation was reduced fecal output. The rabbit remained alert, active and inquisitive. This animal is placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

#1622 (II; 0.3 MKD), #1652 (III; 1 MKD) and #1659 (III; 1 MKD) experienced body weight loss (range of 7.5-11.5% over 12 to 22 days) and had low feed intake (range of 5 to 10 days.) The only clinical observation was reduced fecal output. The rabbits remained bright, alert and inquisitive and were euthanized as scheduled at the end of the study. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

#8698, #8699, #8700, #1661, #1662, #1663, #1664, #1665, #1666, #1667, #1668, #1669, #1670, #1671, #1672, #1674, #1675, #1676, #1677, #1678, #1679 and #1680 ,Group IV (5 MKD) were observed with one or more of the following clinical signs on one or more days of dosage (range of 1 to 12 days): ataxia, salivation, exophthalmia, reactivity to touch and/or decreased activity. All animals appeared normal at the time of dosage on each day of dosage. Some rabbits gained body weight daily, some had reduced body weight gain, some maintained body weight and some lost body weight (range of 3-16% over the dosage period.) Accordingly, some rabbits had good feed intake, some had moderate to fair feed intake and some had low feed intake (range of 2 to 15 days.) Rabbits with low feed intake were provided with timothy cubes. #1664 was euthanized at the time of abortion on GD28. This rabbit was normal at necropsy exam. All other rabbits were euthanized as scheduled at the end of the study, appeared normal at necropsy exam and have live fetuses. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss and/or there may have been some level of discomfort/distress associated with the clinical observations.

Study: #41
Animals: 17 Rabbits
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study of XXX in Rabbits

Guidelines/Regulations:

- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD).

- U.S. Food and Drug Administration. Good laboratory practices for nonclinical laboratory studies, 21 C.F.R. 58.
- Pharmaceutical Affairs Bureau, Ministry of Health, Labour and Welfare. GLP standard ordinance for nonclinical laboratory studies on safety of drugs, MHW Ordinance No. 21; March 26, 1997. Japan.
- OECD Environment Directorate. OECD Principles of good laboratory practices, [C(97)186/Final] (1998); Environmental Health and Safety Division.

Diagnosis: **Seventeen** rabbits from this developmental toxicity conducted in October through November 2006 have been placed in category E as described below

The following rabbits had moderate to severe weight loss while pregnant, reduced feed intake, and necropsy signs associated with the nature of the test article (hemorrhage) in the rabbit and/or death and resorption of fetuses: **#8964 (IV; 150 MKD), #8965 (IV; 150 MKD), #8971 (IV; 150 MKD)** and **#8989 (IV; 150 MKD)** were found dead; **#8962 (IV; 150 MKD), #8969 (IV; 150 MKD), #8970 (IV; 150 MKD), #8972 (IV; 150 MKD), #8974 (IV; 150 MKD), #8977 (IV; 150 MKD)** and **#8979 (IV; 150 MKD)** were euthanized prior to the date of scheduled euthanasia; **#8935 (II;15 MKD)** and **#8955 (III; 45 MKD)** were euthanized on the date of scheduled euthanasia.

The following rabbits had necropsy signs associated with the nature of the test article (hemorrhage) in the rabbit and/or death and resorption of fetuses in the absence of clinical signs prior to being found dead: **#8958 (IV; 150 MKD), #8963 (IV; 150 MKD)** and **#8973 (IV; 150 MKD).** #8963 and #8973 also experienced moderate body weight loss and reduced feed intake.

Rabbit **#8968 (IV; 150 MKD)** had decreased motor activity on the day prior to euthanasia. It is assumed that this may have been associated with some level of discomfort/distress and this animal was therefore categorized as E.

Study: #42
Animals: 11 Rabbits
Type of Study: Oral (Stomach Tube) Dosage Range Non-GU Developmental Toxicity study of XXX in Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Eleven** rabbits from this dosage range-finding developmental toxicity study conducted in October 2006 have been placed in category E as described below.

#5951 (I; vehicle) lost 28.3% body weight from GD9-GD29 and delivered on GD29, the day of scheduled euthanasia. The volume of the twice daily dosing was suspected as a factor in the decreased feed intake for all animals including those in the vehicle group. At all exams, the rabbit had normal behavior and attitude until GD28 when a more calm/quiet attitude was noted. This animals is placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

#7960 (II, 60 MKD), #7961(III; 400 MKD), #7964 (III; 400 MKD), #7965 (III; 400 MKD) and #7968 (IV; 1200 MKD) lost 11.6 to 21.0% body weight over a period of 7 to 21 days and had low feed consumption and scant or no fecal output over the same time period. #7960, #7961, 7964 and #7965 were euthanized at the time of abortion/delivery and #7968 was euthanized when group IV was terminated. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

#7963(III; 400 MKD), #7966(IV; 1200 MKD), #7977(IV; 1200 MKD), #7969(IV; 1200 MKD) and #7970(IV; 1200 MKD) lost up to 14.4% body weight over a period of 2 to 11 days and had low or no feed consumption and scant or liquid fecal output over the same period. In addition to the weight loss and low feed intake, other clinical signs present for up to 7 hours prior to euthanasia included excess salivation, nasal discharge, decreased activity, dehydration, mild-moderate muscle rigidity. These animals were euthanized when each met the criteria established on the third day of dosage for euthanasia (severe muscle rigidity, ataxia, or hyperpnea). These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss and/or there may have been some level of discomfort/distress associated with the clinical observations.

Study: #43
Animals: 3 Rabbits
Type of Study: Oral (Stomach Tube) GLP-Developmental Toxicity Study of XXX in Rabbits

Guidelines/Regulations:

- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) 55A; September, 1994. Rockville (MD).
- U.S. Food and Drag Administration. Good laboratory practices for nonclinical laboratory studies, 21 C.F.R. 58.
- Pharmaceutical Affairs Bureau, Ministry of Health, Labour and Welfare. GLP standard ordinance for nonclinical laboratory studies on safety of dings, MHW Ordinance No. 21; March 26, 1997. Japan.
- OECD Environment Directorate. OECD Principles of good laboratory practices, [C(97)186/Final] (1998); Environmental Health and Safety Division.

Diagnosis: **Three** rabbits from this developmental toxicity study conducted in November through December 2006 have been placed in category E as described below.

#9333 (II; 6 MKD), #9368 (IV; 240 MKD) and #9372 (IV;240 MKD) have been placed in category E for the duration of scant fecal output and un-groomed fur (range 6-12 days), the magnitude and duration of weight loss during gestation (range 12-16% over 14-19 days), the duration of low feed consumption (range 8-12 days), failure to consume the supplemental food items and findings at necropsy examination (#9368 and #9372 only; #9333 was normal at necropsy.) #9333 was euthanized as scheduled at the end of the study. #9368 was euthanized on gestation day 22 due to signs of an impending abortion. #9372 was euthanized on gestation day 26 at the time when a decrease in activity level was first observed.

Study: #44
Animals: 18 Rabbits
Type of Study: Subcutaneous Dosage-Range Developmental Toxicity Study of in Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Eighteen rabbits** from this subcutaneous dosage range-finding study conducted in January through March 2007 have been placed in category E as described below

#6441 (0.4 mg/kg), #6442 (0.4 mg/kg) and #6443 (0.4 mg/kg), experienced acute body weight loss (5.6%-9.7%) over 3 to 6 days and low feed intake over the same period. Reduced fecal output was the only clinical sign. These animals were euthanized as scheduled and were normal at necropsy. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

#784 (0.04 mg/kg), #771 (0.1 mg/kg), #772 (0.1 mg/kg), #773 (0.1 mg/kg), #774 (0.1 mg/kg), #775 (0.1 mg/kg), #787 (0.1 mg/kg), #776 (0.4 mg/kg), #777 (0.4 mg/kg), #778 (0.4 mg/kg), #779 (0.4 mg/kg), #780 (0.4 mg/kg), #790 (0.4 mg/kg), #791 (0.4 mg/kg) and #792 (0.4 mg/kg) experienced acute body weight loss (4%-20%) over 4 to 16 days and fair to low feed intake over the same period. Some of these rabbits had no clinical signs and others had reduced fecal out put. All rabbits except one (#774) completely re-gained the lost body weight, had feed intake improve to a moderate or good level and were euthanized as scheduled. All rabbits were normal at necropsy examination #774 lost 17% body weight over 11 days and was euthanized at the time that decreased activity was observed. This rabbit was normal at necropsy exam. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

Study: #45
Animals: 10 Rabbits
Type of Study: Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of XXX in Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Ten rabbits** from this dosage range-finding developmental toxicity study conducted in April through May 2007 have been placed in category E as described below.

#1316 (100 MKD), #1317 (100 MKD), #1318 (100 MKD), #1319 (100 MKD), #1320 (100 MKD), #1321 (300 MKD), #1322 (300 MKD), #1323 (300 MKD), #1324 (300 MKD) and #1325 (300 MKD) lost 4 -17% body weight over 5 to 19 days (#1316 and #1320 regained all lost weight after the dosage period ended) and had low feed intake for 4 to 18 days. #1321 (V), #1323 (V) and #1325 (V) had scant fecal out put and were found dead at the morning viability checks. #1322 (V) was euthanized at the time that clinical signs were observed. #1324 (V) was euthanized to terminate group V. #1317 (IV) and #1319 (IV) had scant fecal output, aborted and were euthanized. #1316 (IV), #1318 (IV) and #1320 (IV) were euthanized as scheduled at the end of the study. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

Study: #46
Animals: 12 Rabbits
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study of XXX in Rabbits

Guidelines/Regulations:

- U.S. Dept of Health and Human Services Food end Drug Administration on Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD).

- U.S. Food and Drug Administration Good Laboratory practices for nonclinical laboratory studies, 21 C.F.R. 58; lest revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: **Twelve rabbits** from this developmental toxicity study conducted in June 2007-July 2007 have been placed in category E as described below.

#2385 (II, Satellite) was found dead at post dosage check on gestation day 17. There was no body weight loss, no reduction in feed consumption and no adverse signs prior to death. Necropsy examination was consistent with a gavage error.

#2307 (I), #2334 (II), #2361 (IV), #2362 (IV), #2363 (IV), #2364 (IV), #2365 (IV), #2366 (IV), #2367 (IV), #2374 (IV) and #2376 (IV) experienced mild to moderate body weight loss (5-13% over 4 to 13 days) and severe reduction in feed consumption (over 4 to 13 days) during the dosage period. Clinical signs included reduced fecal output. These rabbits were euthanized as scheduled at the end of the study and were normal at necropsy examination. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

Study: #47
Animals: 6 Rabbits
Type of Study: Maximum Tolerated Dosage (MTD) Oral (Stomach Tube) Toxicity and Toxicokinetics Study in Female Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Six rabbits** (all rabbits in groups IV and V) from this maximum tolerated dosage toxicity study conducted in February through March 2007 have been placed in category E as described below.

#360 (400 MKD), #361 (400 MKD), #362 (400 MKD) and #365 (800 MKD) were euthanized as scheduled on study day 8. Body weight loss over seven days ranged from 8.4% to 18.9% and feed intake was fair to low/none over the same period. Scant fecal output was also noted in these rabbits. Immediately prior to scheduled euthanasia following the time of the final blood collection via the ear vein on study day 8, #360 and #365 were pale, lethargic, with ptosis and evidence of external blood loss. Consequently, these two rabbits were immediately euthanized and the final blood collections were done following death. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss and/or clinical signs prior to euthanasia.

#364 (800 MKD) was found dead during the morning viability check on study day 3. No adverse signs were noted prior to death. No body weight was lost and feed intake was reduced to a fair level. This rabbit was conservatively categorized as an E as other animals in the same dose group had experienced clinical signs prior to euthanasia. Since this rabbit died during the night we were not able to definitively say that it had not experienced similar clinical signs prior to death.

#363 (800 MKD) was euthanized in moribund condition on study day 7. Scant fecal output and un-groomed coat were noted for several days prior to euthanasia. Body weight loss from study day 1 to 7 was 13.9% and feed intake was low during the same period. At the time of euthanasia, the rabbit was pale, lethargic and had labored breathing.

Study: #48
Animals: 10 Rabbits
Type of Study: Oral (Stomach Tube) Dosage-Range Developmental Toxicity and Toxicokinetics Study in Rabbits (non-GLP)

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Ten** rabbits from this dosage range-finding developmental toxicity study conducted in March 2007 through April 2007 have been placed in category E as described below.

# 829 (50 MKD), #815 (50 MKD), #817 (100 MKD), #834 (100 MKD), #823 (200 MKD), #824 (200 MKD), #838 (200 MKD), #835 (200 MKD), #836 (200 MKD) and #837 (200 MKD) had zero to low feed consumption during pregnancy (range of duration 6 to 16 days), body weight loss during pregnancy (6.0% to 17.6%), scant fecal output, discolored feces and un-groomed hair coat. Supportive care included the provision of second water sources, dry timothy cubes, timothy cubes moistened with water and daily grooming to minimize the ingestion of hair by the rabbit when grooming. These rabbits were either euthanized due to abortion (#815), euthanized at the recommendation of the veterinary staff due to clinical signs (#823, #824, #838, #836), euthanized as scheduled at the end of the study (#817, #829, #834, #837) or found dead (#835.) These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss and/or clinical signs and/or necropsy findings

Study: #49
Animals: 26 Rabbits
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study in Rabbits (GLP)

Guidelines/Regulations:

- U.S. Dept of Health and Human Services Food end Drug Administration on Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD).
- U.S. Food and Drug Administration Good Laboratory practices for nonclinical laboratory studies, 21 C.F.R. 58; lest revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: **Twenty six** rabbits from this developmental toxicity study conducted in May 2007-June 2007 have been placed in category E as described below

#1978 (IV) was found dead on GD14. Necropsy findings were consistent with gavage error.

#1984 (II), #1987 (III), #1990 (IV), #1992 (IV), #1925 (II), #1934 (II) #1939 (II) #1943 (III), #1948 (III), #1950 (III), #1952 (III), #1954 (III), #1956 (III), #1959 (III), #1961 (IV), #1962 (IV), #1964 (IV), #1965 (IV), #1966 (IV), #1967 (IV), #1968 (IV), #1970 (IV), #1971 (IV), #1973 (IV) and #1975 (IV) experienced body weight loss (3.6%-16.8% over 6 to 20 days) and had low feed intake (4 to 15 days in duration). Fourteen of these rabbits were euthanized as scheduled at the end of the study, four rabbits were euthanized at the time of abortion, one rabbit was found dead at morning viability checks and six rabbits were euthanized by veterinary recommendation when signs of lethargy and/or paleness were observed. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss and/or clinical signs and/or necropsy findings

Study: #50
Animals: 8 Rabbits
Type of Study: Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of XXX in Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Eight** rabbits from this dosage range-finding study conducted in January 2007 have been placed in category E as described below
#4918 (IV, 1000 MKD), #4924 (V, 1500 MKD) and #4925 (V, 1500 MKD) were found dead on the second or fourth day of dosage. Liquid feces and low feed intake were present on the day before death. Weight loss was none or minimal. Necropsy findings included stomach ulcerations, stomach erosions and a red thymus. Viability of fetuses was not determined due the early gestation age. While no adverse behavior changes were apparent prior to the time of discovery of death, the necropsy findings may have been associated with some level of discomfort/distress prior to death.

#4908 (II, 200 MKD), #4909 (II, 200 MKD), #4912 (III, 500 MKD), #4913 (500 MKD) and #4915 (III, 500 MKD) were found dead (#4912), aborted and were euthanized (#4908 and #4913) or euthanized due to clinical signs (#4909 and #4915.) Body weight loss during pregnancy ranged from 16.8 to 17.7 % over 11 to 20 days. Feed intake was low from 10 to 14 days prior to death. Scant fecal output was present in all these rabbits and clinical adverse signs included respiratory rales, un-groomed fur, and paleness. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss and/or clinical signs and/or necropsy findings.

Study: #51
Animals: 5 Rabbits
Type of Study: Intramuscular Reproductive and Developmental Toxicity Study of XXX in Rabbits, Including a Postnatal Evaluation

Guidelines/Regulations:

- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September,1994. Rockville (MD).

- U.S. Dept of Health and Human Services Food and Drug Administration, (CBER). Guidance for Industry: considerations for developmental toxicity studies for preventive and therapeutic vaccines for infectious disease indications. February 2006. Rockville (MD).
- U.S. Food and Drug Administration. Good laboratory practices for nonclinical laboratory studies, 21 C.F.R. 58.
- Pharmaceutical Affairs Bureau, Ministry of Health, Labour and welfare. GLP standard ordinance for nonclinical laboratory studies on safety of drugs, MHW Ordinance No. 21: March 26, 1997 CF.R. 58.
- OECD Environment Directorate. OECD Principles of good laboratory practices, [C(97)186/Final] (1998); Environmental Health and Safety Division.

Diagnosis: **Five rabbits** from this reproductive and developmental toxicity study conducted in October 2006- January 2007 have been placed in category E as described below.

#9848 (0/0.5 mcg/ml), #9854 (0/0.5 mcg/ml), #9863 (15/0.5 mcg/ml), #9868 (15/0.5 mcg/ml) and #9879 (15/0.5 mcg/ml) lost 6.7-10.0% body weight over six to thirteen days and had low feed intake over the same period. The rabbits remained bright, alert and inquisitive and the only clinical signs were reduced fecal output. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss.

Study: #52
Animals: 32 Rabbits
Type of Study: Intramuscular Reproductive and Developmental Toxicity Study of XXX in Rabbits, Including a Postnatal Evaluation

Guidelines/Regulations:

- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September,1994. Rockville (MD).
- U.S. Dept of Health and Human Services Food and Drug Administration, (CBER). Guidance for Industry: considerations for developmental toxicity studies for preventive and therapeutic vaccines for infectious disease indications. February 2006. Rockville (MD).
- U.S. Food and Drug Administration. Good laboratory practices for nonclinical laboratory studies, 21 C.F.R. 58.
- Pharmaceutical Affairs Bureau, Ministry of Health, Labour and welfare. GLP standard ordinance for nonclinical laboratory studies on safety of drugs, MHW Ordinance No. 21: March 26, 1997 CF.R. 58.
- OECD Environment Directorate. OECD Principles of good laboratory practices, [C(97)186/Final] (1998); Environmental Health and Safety Division.

Diagnosis: **Thirty two** rabbits from this reproductive and developmental toxicity study conducted in October 2006 through February 2007 have been placed in category E as described below

Group I (saline control) rabbits #9507, #9514, #9516, #9517, #9519, #9521, #9523, Group II (45 mcg/0.5 ml) rabbits #9525, #9526, #9529, #9531, #9536, #9537, #9538, #9540, #9541, #9548, Group III (saline control) rabbits #9549, #9550, #9553, #9557, #9560, #9563, #9571 and Group IV (45 mcg/ 0.5 ml) rabbits #9573, #9574, #9579, #9581, #9582, #9583, #9585 and #9590 had scant to no fecal output, zero to low feed intake (range of duration 0 to 18 days) and/or body weight loss during pregnancy (0% to 23%.) Supportive care included the provision of a second water source, timothy cubes, timothy cubes re-hydrated with water and certified fruit-flavored treats. These rabbits were found dead (four rabbits), euthanized at the time of abortion (six rabbits), euthanized when decreased activity level was observed (six rabbits) or euthanized as scheduled at the end of the study (sixteen rabbits.) The majority of these rabbits were normal at necropsy examination. Necropsy findings (twelve rabbits) included stomach erosions, pale liver, pale heart, pale kidneys, lungs mottled red and dark red, a cystic kidney and thickened urinary bladder walls. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss and/or clinical signs and/or necropsy findings.

Study: #53
Animals: 17 Rabbits
Type of Study: Intramuscular Reproductive and Developmental Toxicity Study of XXX in Rabbits, Including a Postnatal

Evaluation

Guidelines/Regulations:

- U.S. Dept of Health and Human Services Food end Drug Administration on Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD).
- U.S. Food and Drug Administration Good Laboratory practices for nonclinical laboratory studies, 21 C.F.R. 58; lest revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: **Seventeen rabbits** from this reproductive and developmental toxicity study conducted in March 2007-July 2007 have been placed in category E as described below.

#1012 (saline control), #1022 (saline control), #1024 (saline control), #1034 (25 mcg/0.5 ml), #1036 (25 mcg/0.5 ml), #1037 (25 mcg/0.5 ml), #1039 (25 mcg/0.5 ml), #1067 (saline control), #1068 (saline control), #1072 (saline control), #1079 (saline control), #1082 (25 mcg/0.5 ml), #1095 (25 mcg/0.5 ml), #1097 (25 mcg/0.5 ml), #1098 (25 mcg/0.5 ml), and #1100 (25 mcg/0.5 ml) experienced mild to severe body weight loss (5-18% over 8 to 29 days) and severe reduction in feed consumption (4 to 17 days duration) during the dosage period. Clinical signs included reduced fecal output, soft feces and un-groomed coat. Seven of these rabbits were euthanized as scheduled and all except two were normal at necropsy exam (one had a pale liver and another had an area of redness in the subcutaneous tissue at the most recent injection site.) One rabbit was found dead at the afternoon viability check on gestation day 26. This rabbit was normal at necropsy exam. Eight rabbits (3 saline controls and 3 treated) were euthanized as per the study protocol due to non surviving kits and all except one were normal at necropsy exam (#1097 had an erosion in the stomach.) These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss and/or clinical signs and/or necropsy findings.

#1052 (25 mcg/0.5 ml) was euthanized by veterinary recommendation two days after the study day 15 injection of the left hind limb (quadriceps muscle.) The limb was held in extension beginning a few hours after the injection and animal was able to move about the cage. No obvious discomfort was observed during exams of this limb. A body weight loss of 7% occurred during this time. The rabbit appeared normal at necropsy exam. This rabbit has been placed in E because injury/neuropathy from handling during injection and/or the injection itself cannot be ruled out as the reason for the body weight loss (an indicator of possible pain/distress.)

Study: #54
Animals: 19 Rabbits
Type of Study: Intramuscular Reproductive and Developmental Toxicity Study of XXX in Rabbits, Including a Postnatal Evaluation

Guidelines/Regulations:

- U.S. Dept of Health and Human Services Food end Drug Administration on Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD).
- U.S. Food and Drug Administration Good Laboratory practices for nonclinical laboratory studies, 21 C.F.R. 58; lest revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: **Nineteen rabbits** from this reproductive and developmental toxicity study conducted in June 2007- September 2007 have been placed in category E as described below.

#2204 (saline control; I), #2205 (saline control; I), #2230-2231 (15mcg; II), #2237-2238 (15 mcg; II), #2249 (15 mcg; II), #2253 (15 mcg; II), #2264(saline control; III), #2278-2280 (saline control; III), #2283 (15 mcg; IV), #2291-2292 (15 mcg; IV), #2295 (15 mcg; IV), #6491 (15 mcg; IV), #6495 (15 mcg; IV) and #6497 (15 mcg; IV) experienced mild to severe body weight loss (6 to 27%) and severe reduction in feed consumption (6 to 16 days duration) beginning in early to mid-gestation. Clinical signs included reduced fecal output, soft feces and un-groomed coat. Eight of these rabbits were euthanized as scheduled and all were normal at necropsy exam. One rabbit aborted and was euthanized on gestation day 24. This rabbit appeared normal at necropsy exam One rabbit (treated) was euthanized because all kits were dead at the time of delivery. This rabbit had a pale liver at necropsy exam. Three rabbits (1 control and 2 treated) were euthanized in early lactation (days 1 to 3) when no kits remained alive. Two of these three appeared normal at necropsy exam and the other had a pale liver. Six rabbits were found dead (2 control and 4 treated.) Two of these found dead rabbits appeared normal at necropsy exam. Four of the found dead rabbits had findings at necropsy exam including stomach ulceration, perinasal blood, and pale organs (heart, liver, kidneys and lungs) . These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss and/or clinical signs and/or necropsy findings.

Study: #55
Animals: 6 Rabbits
Type of Study: Intramuscular Dosage-Range Developmental Toxicity Study of XXX in Rabbits

Guidelines/Regulations:

- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry. detection of toxicity to reproduction for medicinal products. (ICH) S5A; September, 1994. Rockville (MD).

Diagnosis: **Six rabbits** from this dosage range developmental toxicity study conducted in May 2007-July 2007 have been placed in category E as described below.

#1521 (50 mcg/25 mcg) and **#1535 (100 mcg/50 mcg)** sustained accidental cuts to the skin when the hair was being clipped away from the intended injection site using electric clippers. One cut was 1.0 cm in length and one cut was 1.5 cm in length. No pain or distress to manipulation of the affected areas was noted during the veterinary exams. The cuts healed completely in 12 and 8 days, respectively. Feed intake and body weight were not affected and the rabbits were euthanized as scheduled at the end of the study. These rabbits have conservatively been placed in category E because the study procedure being performed (hair clipping) resulted in an accidental injury which may have been associated with some level of discomfort/distress.

#1508 (50 mcg/0 mcg), #1512 (50 mcg/0 mcg), #1522 (100 mcg/50 mcg) and #1523 (100 mcg/50 mcg) experienced mild to moderate body weight loss (0-11%) and moderate to severe reduction in feed consumption for 4 to 7 days during the dosage period. Clinical signs included reduced fecal output (1-2 days duration) and un-groomed fur. These rabbits were euthanized as scheduled at the end of the study. #1508, #1522 and #1523 were normal at necropsy examination. #1512 had numerous white areas present on all liver lobes. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss and/or clinical signs and/or necropsy findings.

Study: #56
Animals: 5 Rabbits
Type of Study: Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of XXX in Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Five** rabbits from this dosage range-finding developmental toxicity study conducted in November-December 2006 have been placed in category E as described below.

#3797 (Part A, 2000 MKD), #9601 (Part B, 0 MKD,vehicle), #9618 (Part B, 500 MKD), #9622 (Part B, 1000 MKD) and #9624 (Part B, 1000 MKD) have been placed in category E for the duration of scant fecal out put and/or the magnitude of acute body weight loss and/or the duration of low feed consumption and/or the adverse findings at necropsy examination.

Study: #57
Animals: 10 rabbits
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study of XXX in Rabbits

Guidelines/Regulations:

- U.S. Dept of Health and Human Services Food end Drug Administration on Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD).

- U.S. Food and Drug Administration Good Laboratory practices for nonclinical laboratory studies, 21 C.F.R. 58; lest revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: **Ten rabbits** from the high dosage group (IV) of this developmental toxicity study conducted in January through February 2007 have been placed in category E as described below.

Group IV rabbits **#962, #963, #965, #966, #967, #972, #973, #975, #978** and **#979** have been placed in category E for the duration of zero to scant fecal output (range of 3 to 10 days) and/or the magnitude of acute body weight loss during gestation (range 7.0% to 19.8%) and/or the magnitude and duration of low feed consumption during gestation (range of 7 to 15 days) and/or the high incidence of fetal deaths/fetal resorption (75-100% in all except #973.)

Study: #58
Animals: 13 Rabbits
Type of Study: Exploratory Oral Gavage Range-Finding Developmental Toxicity Study for Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Thirteen rabbits** from this dosage range-finding developmental toxicity study conducted in November through December 2006 have been placed in category E as described below.

#9705(1I1), 9706(111), #9707(IV), #9708(W), #9709(V), #9710(V), #9712(VY), #9714(111), #9715(IV) and #9717(VI) from Part A have been placed in category E for the duration of zero to scant fecal output (range of 1 to 6 days) and/or other clinical observations the day before death or euthanasia and/or the magnitude of acute body weight loss (range 6% to 19%) and/or the magnitude and duration of low feed consumption (range of 1 to 6 days) and the necropsy observations. Stomach erosion and ulceration was noted in each of these rabbits and pleural effusion was also noted in three of these rabbits.

#9676(V) and #9682(VI) from Part B have been placed in category E for the duration of zero to scant fecal output (range of 3 to 8 days) and/or the magnitude of acute body weight loss during gestation (range 17% to 18%) and/or the magnitude and duration of low feed consumption during gestation (range of 10 to13 days) and/or the high incidence of fetal deaths/fetal resorptions (100%.) These rabbits were euthanized at the time of abortion. Behavior and attitude were normal at all times for #9676 and normal for #9682 until the date of abortion and euthanasia when apprehension was noted.
#9673 (IV) from Part B was found dead at morning viability checks and necropsy findings were consistent with gavage error.

Study: #59
Animals: 4 Rabbits
Type of Study: Subcutaneous Developmental Toxicity Study of XXX in Rabbits

Guidelines/Regulations:

- U.S. Dept of Health and Human Services Food and Drug Administration. Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September,1994. Rockville (MD).
- U.S. Food and Drug Administration. Good laboratory practices for nonclinical laboratory studies, 21 C.F.R. 58.
- Pharmaceutical Affairs Bureau, Ministry of Health, Labour and welfare. GLP standard ordinance for nonclinical laboratory studies on safety of drugs, MHW Ordinance No. 21: March 26, 1997 CF.R. 58.
- OECD Environment Directorate. OECD Principles of good laboratory practices, [C(97)186/Final] (1998); Environmental Health and Safety Division.

Diagnosis: **Four** rabbits from this developmental toxicity study have been placed in category E as described below

#407 (I; 0 MKD), #414 (I; 0 MKD) and #471 (IV; 30 MKD) had scabs on the dorsal back ranging in size from 1.0 x 0.3 cm to 1.0 x 0.5 cm and ranging in duration from two to five days. These scabs were not present on the day of arrival and were present before the first dosage. It is likely that these scabs were the result of the clipping of hair done a few days before the start of the dosage period. These rabbits had no other adverse signs, ate well during the entire study and had good feed consumption during the entire study. **#432 (II; 3 MKD)** had a scab (2.0 x 1.5 cm) present at one injection site from gestation day 8 through 19. The scab was no longer present on gestation day 20. This rabbit had no other adverse clinical signs, gained weight daily and had good feed consumption daily. No pain or distress was noted during daily data collection (signs and body weights) or during weekly veterinary evaluation. These rabbits have been conservatively placed in category E because it can be presumed that the inflammatory process resulting in scab formation of the sizes noted was associated with some level of discomfort/distress at some point during the formation.

Study: #60
Animals: 12 Rabbits
Type of Study: Oral Dose-Range Developmental Toxicity Study in Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Twelve rabbits** from this dosage range-finding developmental toxicity study conducted in February through March 2007 have been placed in category E as described below.

Part A Rabbits. **#305 (100 MKD)** was found dead prior to administration of the fifth dosage. No adverse clinical signs were observed. There was body weight loss of 4.8% over two days and several days of low feed intake Necropsy observations included yellow pancreas, yellow abdominal fat and yellow mesentery. **#306 (100 MKD)** was euthanized as scheduled on the sixth day after the start of dosage. Weight loss was 11.5% over 4 days and feed intake was low during this same time. **#308 (300 MKD)** was found dead during the morning viability check prior to administration of the fourth dosage. No adverse clinical signs were observed. Weight loss was 7.6% over two days and feed intake was low. Necropsy observations included red intestinal mucosa, thickening of the liver, yellow abdominal organs, pale heart and fluid in the thoracic and abdominal cavities. **#307 (300 MKD)** was euthanized as scheduled on the sixth day after the start of dosage. Weight loss was 9.0% over the last three days of dosage and feed intake was low. **#311 (70 MKD)** was found dead during the morning viability check on the sixth day after the start of dosage. Scant fecal output was noted for several days, feed intake was low and 10% weight loss occurred. At necropsy, brown fluid was present in the thoracic cavity. **#310 (70 MKD) and #312 (70 MKD)** were euthanized as scheduled on the sixth day after the start of dosage. Weight loss was 6.7 and 9.2%, respectively, over study days 2 through 5 when feed intake was low and scant fecal output was noted. Both rabbits gained weight on study day 5 through 6. . These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss and/or clinical signs and/or necropsy findings.

Part B Rabbits. **#572 (60 MKD)** was found dead at the 3 hour post dosage check on gestation day 11. This was the first death in Part B of this study. Feed intake was low two days prior to death and weight loss was 4.9%. Decreased activity level was noted prior to death at the one hour and two hour post dosage checks. At necropsy, brown fluid was present in the thoracic cavity, the liver was thickened and all fetuses were dead. **#575 (60 MKD)** was examined on gestation day 11 for a decrease in activity level after dosage administration. Activity level improved over a thirty minute period. This rabbit was found dead during the morning room check the next day. Feed intake was at a fair level for two days and the body weight was reduced by 4.9% during the same period. At necropsy, brown fluid was present in the thoracic and abdominal cavities and all fetuses were dead. **#571 (60 MKD)** was found dead prior to dosage on gestation day 16. Un-groomed hair coat was the only clinical sign present prior to death. Feed intake was low for two days and body weight was reduced by 10.9% over seven days. At necropsy, blood was present in the thoracic and abdominal cavities and all fetuses were resorbed. **#574 (60 MKD)** was found dead during the morning room check on gestation day 17. No adverse signs were observed by the study staff or veterinary staff. Feed intake was at a fair level for two days and the body weight was reduced by 4.0% during the same period. Subcutaneous blood was present in the ventral thoracic and abdominal areas at necropsy and all fetuses were resorbed. **#568 (30 MKD)** had low feed intake for 15 days. 11.5% body weight was lost GD9-13, body weight was maintained GD13-17 and 15.2% was lost GD17-29. In addition to the dry timothy cube that all rabbits in this group received, this rabbit also received a timothy cube moistened in water. This rabbit was also groomed daily to help minimize the ingestion of hair during self grooming. Scant urine output was noted on four days and discolored urine on one day. This rabbit was euthanized, as scheduled, at the end of the study. There was a small mass on one liver lobe at necropsy and all fetuses were resorbed. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss and/or clinical signs and/or necropsy findings.

Study: #61
Animals: 7 Rabbits
Type of Study: Oral Developmental Toxicity Study in Rabbits

Guidelines/Regulations:

- U.S. Dept of Health and Human Services Food end Drug Administration on Guideline for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD).

- U.S. Food and Drug Administration Good Laboratory practices for nonclinical laboratory studies, 21 C.F.R. 58; lest revised April 1, 2002; U.S. Federal Government Archives.

Diagnosis: **Seven rabbits** from this developmental toxicity study conducted in May–June 2007 have been placed in category E as described below.

#2061 (IV), #2069 (IV), #2070 (IV), #2086 (V) and #2089 (V) lost 17-22% body weight over 11-16 days of gestation and had low feed intake for 7-12 days. Clinical signs in these animals were scant fecal output and un-groomed fur. #2070 and #2089 were euthanized as scheduled at the end of the study. #2089 was normal at necropsy exam and all fetuses were resorbed. #2070 had an adhesion between one liver lobe, the stomach and the abdominal wall and all fetuses were resorbed. #2086 was euthanized on the day of abortion. This rabbit as normal at necropsy exam and all fetuses were resorbed. #2061 and #2069 were euthanized by veterinary recommendation when additional clinical signs were first observed. #2061 had an adhesion of the abdominal fat, the stomach and the abdominal wall and all fetuses were resorbed. #2069 had white areas on the lungs and the gall bladder and all fetuses were resorbed. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss and/or clinical signs and/or necropsy findings.

#2092 (V) was euthanized as scheduled at the end of the study. Necropsy exam showed an adhesion of the spleen, stomach and abdominal fat. One fetus was alive and two were resorbed. This rabbit had no adverse signs, had good feed intake daily and experienced no body weight loss. This animal is being conservatively categorized an E as other animals in the same dose group had clinical signs that might be associated with some level of discomfort/distress.

#2096 (V) was found dead on gestation day 17 during the morning viability check. No adverse clinical signs present prior to death. 7.8% body weight was lost over nine days and feed intake was low for 4 days prior to death. Necropsy exam showed a pale heart, green fluid in the chest cavity and all fetuses were resorbed. This animal is placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss and/or clinical signs and/or necropsy findings.

Study: #62
Animals: 13 Rabbits
Type of Study: Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of XXX in Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Thirteen rabbits** from this dosage range-finding developmental toxicity study conducted in July and August 2007 have been placed in category E as described below.

The thirteen rabbits were from dosage groups II, III and IV (50:100 MKD, 75:100 MKD and 100:100 MKD.) These rabbits had reduced feed intake (low to fair level for 4 to 22 days) and body weight loss (9-23% over 5 to 24 days.) In most animals, feed intake and body weight improved after the dosage period ended. Clinical signs included reduced fecal output, soft feces, decreased activity (one animal), ataxia (one animal) and excess salivation (one animal.) Two rabbits in group IV were found dead, one at morning viability checks and one at post dosage check. One rabbit in group III was euthanized per veterinary recommendation due to moribund condition and this animal had no adverse clinical signs present prior to this time. Ten rabbits were euthanized as scheduled at the end of the study. Necropsy observations included normal (no adverse observations), stomach erosions, lungs mottled red, pale liver, red thymus and spongy lungs and resorption of some fetuses. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss and/or clinical signs and/or necropsy findings.

Study: #63
Animals: 4 Rabbits
Type of Study: Oral (Stomach Tube) Developmental Toxicity Study of XXX in Rabbits

Guidelines/Regulations:

- U.S. Dept of Health and Human Services Food end Drug Administration. Guideline foe Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September, 1994. Rockville (MD).
- U.S. Food and Drug Administration Good laboratory practices for nonclinical laboratory studies, 21 C.F.R 58.
- Pharmaceutical Affairs Bureau, Ministry of Health, Labour and Welfare. GLP standard ordinance for nonclinical laboratory studies on safety of drugs, MHW Ordinance No. 21; March 26, 1997. Japan.

Diagnosis: **Four rabbits** from this developmental toxicity study conducted in December 2006 have been placed in category E as described below

#9902 (vehicle) and **#9912 (vehicle)** had evidence of gavage error at necropsy exam

#9910 (vehicle) was euthanized as scheduled at the end of the study (GD29.) This rabbit lost 20.4 % body weight from GD13 to GD29 and had low feed intake from GD15 to GD29. The only clinical observation was scant fecal output from GD17 to 28. Supportive care measures included provision of a dry timothy cube daily, a timothy cube rehydrated in water daily and daily grooming to minimize the ingestion of hair by the rabbit while grooming during low feed intake. The rabbit's attitude and behavior remained normal. At necropsy, there was a dark area on one of the rabbit's liver lobes. There were 11 live fetuses and 1 resorption. This animal is being conservatively categorized an E as other animals in the same dose group had clinical signs that might be associated with some level of discomfort/distress.

#9932 (250 MKD) was euthanized as scheduled at the end of the study (GD29.) This rabbit lost 14.8% body weight from GD7 to GD26 and had low feed intake from GD10 to GD26. Feed intake improved to a moderate level from GD26 to GD29 and 6.5% body weight was gained during this time. The only clinical observation was scant fecal output from GD15 to 28. Supportive care measures included provision of a dry timothy cube daily and a timothy cube rehydrated in water daily. The rabbit's attitude and behavior remained normal. At necropsy, the rabbit was normal. There were 11 live fetuses. . This animal is being conservatively categorized an E as other animals in the same dose group had clinical signs that might be associated with some level of discomfort/distress.

Study: #64
Animals: 12 Rabbits
Type of Study: Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of XXX in Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Twelve rabbits** from Part A of this dosage range-finding study conducted in December 2006 - January 2007 have been placed in category E as described below.

#89 (480 MKD) was euthanized per veterinary recommendation on study day 7 approximately 6 hours after dosage administration. Necropsy examination was consistent with gavage error.

#86 (360 MKD), #82 (480 MKD) and #88 (480 MKD) were euthanized on study day 14 for clinical signs including body weight loss and reduced feed intake. Weight loss ranged from 7%-9% over 7 to 14 days and feed intake was markedly reduced compared to that of animals in group 1. Scant fecal output and signs of transient, mild sedation were present on one to two occasions in the days prior to euthanasia. # 82 had pale kidneys at necropsy exam and #86 and #88 were normal at necropsy exam. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss and/or clinical signs and/or necropsy findings.

#6432 (240 MKD), #6433 (240 MKD), #6434 (240 MKD), #6436 (300 MKD), #6437 (300 MKD), #6438 (360 MKD), #6439 (360 MKD) and #6440 (360 MKD) experienced acute body weight loss (1%-10% over 1 to 6 day) and low feed intake (1 to 4 days). #6433 and #6439 died quickly at the time that clinical signs first appeared. #6432, #6436 and #6440 were euthanized when signs in addition to the weight loss and low feed intake occurred. #6434 and #6438 were euthanized as scheduled at the end of the study. #6438 had weight loss and low feed intake only (no clinical signs) and #6434 experienced a period of transient sedation the day before euthanasia. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss and/or clinical signs and/or necropsy findings.

Study: #65
Animals: 6 Rabbits
Type of Study: Oval (Stomach Tube) Dosage Range Developmental Toxicity Study of XXX in Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies, and by that requirement, a maximum tolerated dose (MTD) is required to be included in the full study to assess the safety of the test material. This dosage-range study is being done to determine dosage selection for future studies that will be based on U.S. Department of Health and Human Services Food and Drug Administration: Guidelines for Industry: detection of toxicity to reproduction for medicinal products, (ICH) S5A; September 1994, Rockville, MD. These guidelines require that dosages produce some maternal toxicity. Conducting the dosage range study prior to a full study, allows the determination of a toxic dose acceptable while only using a few animals. Without conduct of this dosage-range study prior to the required full developmental toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Six rabbits** from Part B of this dosage range-finding study conducted in January through February 2007 have been placed in category E as described below.

#519 (60 MKD), #521 (180 MKD), #522 (180 MKD), #523 (180 MKD), #524 (180 MKD) and #525 (180 MKD) experienced body weight loss (5%-14% over 4 to 13 days) and low feed intake (duration of 3 to 13 days). All were provided with timothy cubes and additional water sources. #521, #522, #524 and #525 were euthanized when clinical signs were first observed. All animals except #524 were normal at necropsy exam. (#524 has a stomach ulcer present at necropsy exam.) #523 was found dead on GD13 and the liver was pale and thickened. #519 was euthanized as scheduled at the end of the study. Scant fecal output was the only clinical sign. This rabbit consumed the provided timothy cubes (BW loss was 14% over 13 days) and was also groomed daily to minimize the ingestion of loose hair during grooming. These animals are placed in category E due to the possibility of distress/discomfort from test article exposure resulted in the decreased feed intake and subsequent body weight loss and/or clinical signs and/or necropsy findings.

CHARLES RIVER LABS PRECLINICAL SERVICES – (Nevada - Site #005)

Study: #66
Animals: 1 Primate
Type of Study: General Toxicity Study, a 39 week toxicity study of XXX administered by nasal gavage to Cynolmolgus monkeys with a 4 week recovery period.

Guidelines/Regulations:

- Supports IND application as required by FDA section 21 CFR 312.21 8 iia, ICH M# guidelines (CPMP/ICH/286/95, CPMP/SWP/1042/99corr), and OECD Guideline 417 Toxicokinetics

Diagnosis: **One primate** - Post dosing animal was having complications breathing. Animal died while being given supportive care. This was a dosing accident. Necropsy of this animal revealed a mass near the left tracheal bifurcation area that appeared to be a chronic condition causing displacement of the trachea where it divides. Due to this displacement if a nasal gavage tube were placed in this area it would have appeared to have been in the stomach (there would have been negative suction pressure on the NG tube)

Study: #67
Animals: 11 Dogs
Type of Study: Seven Day Repeat Dose Toxicity Study of XXX Administered by Subcutaneous Route to Beagle Dogs

Guidelines/Regulations:

- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

Diagnosis: **All eleven dogs** were observed with dose-dependent signs of deep-tissue inflammation/swelling at the injection site(s) and skin thickening. In this 7-day study, the first observation was noted on Study Day 4 (high-dose group), with the mid-high dose observations seen on Study Day 5, and low-dose observed on Study Day 6. All animals were euthanized on Study Day 7. Special care was taken to avoid the swollen areas of the neck, and there were no other clinical abnormalities (dogs continued to eat, drink and behave normal). These animals are being conservatively categorized as E since there was the possibility that some level of discomfort/distress was associated with the localized swelling at the injection site.

Study: #68
Animals: 4 Dogs
Type of Study: A Feasibility and Tolerance Study of Intranasal Administration of XXXX in Beagle Dogs

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies. This feasibility and tolerance study is being done to determine dosage selection for future studies that will be based on the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals. Without conduct of this study prior to the required full toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Four dogs** - For the IACUC proposal review, information was provided by the Sponsor that indicated to the Study Director and IACUC members that the administration of the test article would not cause pain and/or distress to the animals. However, the sponsor provided additional information after the in-life portion of this study was completed. The new information regarding clinical trials of the administration of the test article at this flow rate indicates that humans reported a burning sensation through the nose. With this new information, it could be considered that the administration of the test article may have been associated with some level of discomfort/distress if administration of the test article to the dog was similar to the reported human experience.

During the in-life phase of the study, no animal was noted to be in pain and/or distress, but because three of four animals struggled during dosing, the flow rate was reduced. The nasal mucosa scores indicated "0" for all observations, with the exception of Female #10258, in which erythema was barely perceptible ("1") on Days 6, 7, and 8. This animal was noted to have struggled during dosing on Study Day 5. The Staff Veterinarian examined the animal's right nostril and observed a slight amount of dry red material. The Technical Staff was instructed to continue to monitor the animal, and no blood was observed by either Technical Staff or Staff Veterinarian. The Staff Veterinarian determined that the animal may have received slight injury to the nostril from the apparatus during the struggle.

The animals did not exhibit any clear signs of pain and/or distress. However, since we cannot definitively say that the administration of the test material to dogs results in a different experience than that reported in man, we have conservatively categorized these animals as E.

Study: #69
Animals: 3 Dogs
Type of Study: Rising-Dose and Multiple-Dose Tolerance Study of XXX Administered by Oral Capsule in Beagle Dogs.

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies. This dose range and tolerance study is being done to determine dosage selection for future studies that will be based on the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals. Without conduct of this study prior to the required full toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: All **three dogs** were noted as thin, with decreased activity, and/or inappetence.
The animals were given feed and water supplements, and the dose administration was lowered and/or halted. Animal #10140 was removed from study and euthanized on Study Day 11, after supportive care did not improve the health of the animal. Animals #10139 and 10141 were found dead prior. These animals are categorized as E because clinical signs may have been associated with some level of discomfort/distress that resulted from exposure to the test material.

Study: #70
Animals: 2 Dogs
Type of Study: A Nine Month Oral Toxicity and Toxicokinetic Study with a 3 Month Recovery Period in Beagle Dogs.

Guidelines/Regulations:

- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

Diagnosis: **Two dogs** - Animal #740 and Animal #791 had clinical signs consistent with gavage error. Both animals died rapidly, prior to having time to euthanize them, therefore they have been categorized as E even though the intent was euthanasia upon recognition of clinical signs of dosing error.

Study: #71
Animals: 6 Dogs
Type of Study: A Seven Day Toxicity and Toxicokinetic Study Administered by Oral Gavage to Beagle Dogs.

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies. This dose range study is being done to determine dosage selection for future studies that will be based on the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals. Without conduct of this study prior to the required full toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Six Dogs** - After the first dose administration on study Day 1, these animals vomited excessively for approximately 2 hours postdose. When the animals were re-checked shortly after the vomiting subsided, they were clinically normal. The dosing was halted, the animals were given a washout period, and the dose administration levels were lowered. The study then restarted on Study Day 6 at the lowered dose levels. These dogs have been conservatively categorized as E as it is possible that the duration of vomiting (multiple times over two hours) may have been associated with some level of discomfort/distress.

Study: #72
Animals: 2 Dogs
Type of Study: 14 Day Toxicity and Toxicokinetic of XXX a\Administered by Oral Gavage to Beagle Dogs

Guidelines/Regulations:

- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

Diagnosis: **Two dogs** - Animal #10243 was found to have poor skin turgor, loose watery feces, decreased activity, thin, and general malaise on study Day 8. Animal #10249 was found to have poor skin turgor and decreased activity on Study Day 5. Both animals were found dead on Study Day 9. Both animals were treated with SubQ) lactated ringers solution and offered both canned feed and oral electrolytes, as well as Nutrical supplementation . The dosing was also suspended for both animals. The animals' health was expected to improve with the dose suspension and supportive care. Even though the animals were treated they did not improve. They were categorized as E because both were unexpectedly found dead with prior clinical signs. It is not possible to definitively say that the animals did not experience some level of discomfort/distress/pain prior to dying since the death was not observed.

Study: #73
Animals: 1 Dog
Type of Study: Oral rising-dose tolerance study of XXX by oral capsule in Beagle dogs

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies. The results from this study will be used to establish dose levels for non-rodent studies of longer durations, including single dose and multiple dose studies, as required for IND submission as noted by International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals.

Diagnosis: **One Dog -**
On Study Day 5, post-ictal behavior was observed and consistent with seizure. The Veterinarian instructed the staff to monitor very closely, offer oral electrolytes SID until improved, and also requested a suspension of dosing from the Study Director. The Animal's health was expected to improve with supportive care, which it did, and remained on study until termination on Study Day 7. Although a seizure was not observed, this animal is being conservatively categorized as an E since it exhibited clinical sings consistent with post-ictal behavior and therefore on can not definitively say that the animal did not experience at least some level of discomfort/distress that may have been associated with a seizure.

Study: #74
Animals: 2 Dogs
Type of Study: Seven Day Repeat Dose Range Finding Toxicity Study of XXX Administered by Oral Capsule to Beagle Dogs

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies. The results from this study will be used to establish dose levels for non-rodent studies of longer durations, including single dose and multiple dose studies, and a maximum tolerated dose when administered for 7 days as required for IND submission as noted by International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals.

Diagnosis: Two dogs - Seizure was observed by the Technical Staff, and the Veterinary Staff were notified. The first observation was noted on Study Day 4 (Mid-high-dose group); this animal was monitored closely and was clinically normal on Study Day 5. The same observation in the mid-dose Group was noted on Study Day 6; this animal was monitored closely and was clinically normal on Study Day 7.
Although the animals did not exhibit any adverse clinical signs, other than the seizure, these animals have been conservatively categorized as E since it is possible that the seizure was associated with some level of discomfort/distress.

Study: #75
Animals: 1 Dog
Type of Study: Five Day Repeated Dose Toxicity Study Administered by Intravenous Injection to Beagle Dogs with a 23 Day Recovery Period

Guidelines/Regulations:

- Preclinical GLP safety studies in animals are required by most regulatory authorities to ensure the safe use of drug products. Refer to FDA-21-CFR 312.23(a)(8) and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

Diagnosis: **One Dog -** Inappetence, decreased activity, abnormal stool, and vomitus were observed beginning on Study Day 3. On Study Day 5 the animal's condition deteriorated rapidly, and it died before euthanasia could be administered. This animal has been categorized as E due to the clinical signs observed and rapid progression to death.

Study: #76
Animals: 4 Rabbits
Type of Study: : A Feasibility and Tolerance Study of Intranasal Administration of XXXX in Rabbits

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies. This feasibility and tolerance study is being done to determine dosage selection for future studies that will be based on the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals. Without conduct of this study prior to the required full toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: Four Rabbits For the IACUC proposal review, information was provided by the Sponsor that indicated to the Study Director and IACUC members that the administration of the test article would not cause pain and/or distress to the animals. However, the sponsor provided additional information after the in-life portion of this study was completed. The new information regarding clinical trials of the administration of the test article at this flow rate indicates that humans reported a burning sensation through the nose. With this new information, it could be considered that the administration of the test article may have been associated with some level of discomfort/distress if administration of the test article to the rabbit was similar to the reported human experience.

During the in-life phase of the study, no animal was noted to be in pain and/or distress, but one male (#10069) was observed to have abnormal breathing sounds and bleeding from the left nostril on Study Day 4. The Staff Veterinarian examined the animal, and after discussion with the Study Director, the animal was not dosed. However, on Study Day 5, the animal was breathing normally, and no blood was present. The animal was dosed, and did not exhibit any adverse reaction for the duration of the study. However, nasal scores indicated slight erythema present beginning on Study Day 6 through Study Day 11 and desquamation (scaling or flaking of dermal tissue) present from Study Day 7 through Study Day 11. No other animal on study was observed with adverse signs. Nasal scores of desquamation and/or slight erythema were observed beginning on Study Day 5, in all four animals on study. The duration of these scores varied among each animal.

The animals did not exhibit any clear signs of pain and/or distress. However, since we cannot definitively say that the administration of the test material to rabbits results in a different experience than that reported in man, we have conservatively categorized these animals as E.

Study: #77
Animals: 1 Swine
Type of Study: Comparative Pharmacokinetic Study of Two Test Articles Administered by IV and IM injection to Pigs
Guidelines/Regulations:

- Refer to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

Diagnosis: **One swine** - Animal #2689 was found dead in the sling during the IV dose administration and submitted to necropsy on Study Day 15. Clinical observations noted prior to being found dead were skin discolored, blue; swelling; and material around eye(s), black. The Pathologist's report for this animal indicated respiratory distress. The animal is being categorized as an E based on the pathology report and that it is possible that some level of discomfort/distress may have occurred at the time of death.

Study: #78
Animals: 4 Swine
Type of Study: A comparative Pharmacokinetic Study of Four Development Lots Administered Subcutaneously in Mini-Pigs.

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies. This study is being done to determine formulation selection for future preclinical animal studies (as well as human studies) that will be based on the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals. Without conduct of this study prior to the required full toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Four swine** - Activity decreased; inappetence, soft stool; depression; and shivering. These signs were expected to be of short duration. All animals received a dose of the test article on Study Day 1 only. The signs were observed between Study Days 3 and 6 for all animals, and within two days, significant improvement was seen, and by Study Day 11, all animals were clinically normal. These animals are being categorized as E as it is possible that some level of discomfort/distress was associated with the observed clinical signs.

Study: #79
Animals: 1 Swine
Type of Study: A 90 Day Dermal Toxicity of XXX with a 14 Day Interim Sacrifice in Hanford Pigs

Guidelines/Regulations:

- This study was required by the FDA after a pre-IND with the sponsor. Refer to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for

Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

Diagnosis: **One Pig -** After the blood collection on Study Day 90, Animal#4533 was observed by the Laboratory Animal Technician to have black material around its eyes, decreased activity, and appeared to be gasping. The animal died before treatment could be administered. The animal died before supportive care or euthanasia could be administered. Even though the intent was to euthanize the animal based on clinical signs, because it died prior to being euthanized this animal is conservatively categorized as E.

Study: #80
Animals: 1 Swine
Type of Study: A 9 month Toxicity Study of XXX Administered by the Dermal Route in Mini-Pigs

Guidelines/Regulations:

- The ICH S4 guidelines require certain studies of certain durations to support clinical trail dosing. Refer to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, S4 Duration of Chronic Toxicity Testing in Animals (Rodent and Non-Rodent Toxicity Testing)
- Refer to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

Diagnosis: One Pig - Broad areas of scabbing and erythema along dorsum; pain on palpation. Dose administration was suspended and the animal was monitored. The animal's condition improved and was completely healed 8 days after dose suspension.

CHARLES RIVER LABS PRECLINICAL SERVICES – (Massachusetts)
Southbridge – Site #003
Worcester –Site # 013
Shrewsbury –Site # 022

IACUC-APPROVED EXCEPTIONS TO REGULATIONS AND STANDARDS

The IACUC and the Attending Veterinarian must approve exemptions from non-human primate environmental enhancement plans and dog exercise activities. Monitoring of these animals during the period that they are exempted is performed by the technical staff with oversight from the Veterinary Staff to ensure that the animals do not exhibit stereotypic behaviors that are detrimental to their overall health and well-being. The following exceptions to standards/regulations were approved by the IACUC during this reporting period.

Species: Macaca sp. (Cynomolgus and/or Rhesus)
Number: 276
All animals were on metabolism and pharmacokinetics studies and may have been used on more than one study. Pair housing, environmental enrichment devices inside the cage and/or dietary restrictions (no fruit peels or peanut shells) were withheld after dose administration for 1-15 days during sample collection. Environmental enrichment devices were allowed outside the cage. External stimuli such as radios, televisions, and conspecific visualization, olfactory and auditory stimulation were provided.

Species: Macaca sp. (Cynomolgus)
Number: 444
Exemption: 291 cynos were exempted for 2-29 days, 44 cynos were exempted 43 days, 43 cynos were exempted for 120 days, and 66 cynos exempted 183 days. All animals were on toxicology studies. Pair housing was exempted after dose administration, as defined above, during sample collection. Environmental enrichment devices and external stimuli such as conspecific visualization, olfactory and auditory stimulation were provided.

Species: Macaca sp. (Cynomolgus or Rhesus)
Number: 48 cyno; 9 rhesus
Animals were on pharmacology or surgical studies. Animals on pharmacology studies may have been used on more than one study. Pair housing was exempted post-surgery to facilitate recovery. Pair housing was exempted after dose administration for up to 15 days during sample collection. Environmental enrichment devices and external stimuli such as radios, televisions, and conspecific visualization, olfactory and auditory stimulation were provided.

Species: Canis familiaris (Dog)
Number: 215
All animals were on metabolism and pharmacokinetics studies and may have been used on more than one study. Pair housing and/or exercise was withheld after dose administration for 1-15 days during sample collection. The square footage of the caging met all requirements for housing the animals, however, it did not meet the additional space needs to eliminate the requirement for exercise outside of the cage. The animals were observed daily for signs of distress from lack of exercise during the exemption period. No animals were noted to be adversely affected during this period.

Species: Canis familiaris (Dog)
Number: 358
Exemption: 134 dogs were exempted for 12-17 days, 72 dogs were exempted 25-28 days, 44 dogs were exempted 43 days, and 108 dogs were exempted 57 days. All animals were on toxicology studies. Pair housing and/or exercise were exempted during dose administration and sample collection. The square footage of the caging met all requirements for housing the animals, however, it did not meet the additional space needs to eliminate the requirement for exercise outside of the cage. The animals were observed daily for signs of distress from lack of exercise during the exemption period. No animals were noted to be adversely affected during this period.

Species: Canis familiaris (Dog)
Number: 70
Animals were on pharmacology or surgical studies. Animals on pharmacology studies may have been used on more than one study. Pair housing was exempted post-surgery to facilitate recovery. Pair housing and/or exercise was exempted after dose administration for up to 15 days during sample collection or post-surgery for up to 35 days to facilitate recovery. The square footage of the caging met all requirements for housing the animals, however, it did not meet the additional space needs to eliminate the requirement for exercise outside of the cage. The animals were observed daily for signs of distress from lack of exercise during the exemption period. No animals were noted to be adversely affected during this period.

Study: #81
Animals: 1 Primate
Type of Study: Evaluate Toxicological Potential of Test Article After 90 Day Oral Administration

Guidelines/Regulations:

- FDA 21 CFR Part 312 investigational new drug application section 312.23 subpart B 5 (ii).

Diagnosis: **One Primate** – Animal was showing signs of hypothermia, poor body condition score (1/5) and dehydration. Supportive care in the form of fluids and supplemental heat source were provided. The monkey did recover and continued to the end of the study. This animal is categorized as an E because of the possibility that test article exposure was associated with some level of discomfort/distress that subsequently resulted in decreased appetite and loss of body weight/poor body condition.

Study: #82
Animals: 3 Primates
Type of Study: Dose escalation and repeat-dose study in order to determine the dose levels for a 28 - day toxicology study

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies. This dose range study is being done to determine dosage selection for future studies that will be based on the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals. Without conduct of this study prior to the required full toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **Three Primates** - Clinical signs for the monkeys were dehydration, anorexia, hunched posture. Despite supportive treatment for the clinical signs (fluids administered SC and supplemental nutritional support). While the conditions did improve, they did not resolve 100%. However, their condition did not require early euthanasia. These animals were categorized as E based on clinical signs and failure of treatment to resolve the condition 100 %.

Study: #83
Animals: 2 Primates
Type of Study: Oral toxicity study

Guidelines/Regulations:

- 21 CFR part 312 investigational new drug application section 312.23 subpart 5B

Diagnosis: **Two Primates** - Animals were showing clinical signs of lethargy, recumbancy, icterus, dehydration, scant feces and food consumption, and hunched posture. Despite being administered supportive therapy (fluids, extra heat source, extra nutritional supplement), monkeys condition deteriorated and animals were euthanized. These animals were categorized as E based on clinical condition failure to improve with treatment and subsequent euthanasia.

Study: #84
Animals: 19 Dogs
Type of Study: Oral Dose Range Finding and Toxicokinetic Study in Dogs

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies. This dose range study is being done to determine dosage selection for future studies that will be based on the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals. Without conduct of this study prior to the required full toxicity studies, larger numbers of animals may be needed for the full study.
- 21 CFR Part 312 IND application section 312.23 subpart B5 (ii)

Diagnosis: **Nineteen Dogs** - Moderate to severe lethargy, pale and tacky mucous membranes, increased heart rate, increased respiratory effort, diarrhea and vomiting were observed in animals. Clinical signs varied from hours to 2 days. Delay in performing euthanasia to relieve pain and distress occurred in order to perform additional study procedures and data collection. Justification based on scientific basis and needs of achieving the aim of the study. Subcutaneous fluids and supplemental food were administered to some animals.

Three of the animals demonstrated signs of aspiration post oral dosing and were euthanized. Final study data was collected prior to euthanasia.

Study: #85
Animals: 1 Dog
Type of Study: Pharmacokinetic study

Guidelines/Regulations:

- Guidance -M3 Nonclinical Safety Studies:, July 1997, Federal Register, 25 Nov 1997 (62 FR 62922.

Diagnosis: **One Dog** - Animal was noted as mildly dehydrated and lethargic in afternoon, approximately 36 post dosing. Supportive care in form of subcutaneous fluids were administrated. Animal found dead next morning, approximately 48 hours post dose. This animal is conservatively categorized as an E because even though clinical signs were treated the animal was found dead the next morning. As death was not observed, one can not definitively state that the animal did not experience some level of discomfort/distress/pain when it died.

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Study: #86
Animals: 1 Swine
Type of Study: Dermal

Guidelines/Regulations:

- FDA Redbook
- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

Diagnosis: **One Swine** – Intermittent convulsions in a single animal that recovered immediately following onset. This animal is categorized as E because it is possible that some level of discomfort/distress was associated with the intermittent convulsions that resolved without treatment.

Study: #87
Animals: 2 Rabbits
Type of Study: Evaluate Potential Toxicity of Test Article When Administered via Ocular Route for 28 Days in Rabbits

Guidelines/Regulations:

- FDA Redbook
- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

Diagnosis: **Two Rabbits** – One animal had weight loss of 18.6% through day 18 of the study, the other had weight loss through study day 15. Supportive care was provided in the form of yogurt for nutrient value as well as water. Animals were found dead on day 21 and day 17, respectively.. Animals were categorized as E due to weight loss (assume test article exposure may have resulted in some level of discomfort/distress that resulted in inappetance and subsequent weight loss) and having been found dead. Since death was not observed we cannot definitively say that the animal did not experience some level of discomfort/distress/pain when it died.

Study: #88
Animals: 6 Rabbits
Type of Study: 28 Day Oral Toxicity Study in Rabbits

Guidelines/Regulations:

- FDA Redbook
- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

Diagnosis: Six Rabbits – Animal experienced severe inappetence which resulted in acute body weight loss. Animals were provided nutritional supplements of lettuce and Nutrical in an effort to restart the animals' appetites. Several animals appeared to recover over time; therefore, these animals were allowed to remain on test with supplements such as lettuce, high fat supplement until weight loss forced moribund euthanasia in some cases. However, moribund euthanasia was conducted when no recovery for several animals was evident.

Study: #89
Animals: 6 Dogs
Type of Study: Oral Toxicity

Guidelines/Regulations:

- OECD Guideline 407
- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

Diagnosis: **Six Dogs** – Animals experienced acute weight loss and prolonged gastroenteritis. Supportive care was provided in the form of Nutrical, water bowls, ice cubes, towels and heat lamps.

Study: #90
Animals: 4 Dogs
Type of Study: 28 Day Oral Dosing of XXX and 14 Day Recovery

Guidelines/Regulations:

- OECD 407
- FDA Redbook
- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

Diagnosis: **Four Dogs** – Animals experienced numerous days of vomiting, dehydration, pyrexia, unexplained lameness (one animal), and decreased food consumption. Supportive care was provided in the form of towels, water bowls, canned diet, nutria-cal, subcutaneous fluids.

Study: #91
Animals: 2 Dogs
Type of Study: Oral Toxicity Study

Guidelines/Regulations:

- FDA
- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

Diagnosis: **Two Dogs** – One dog was reported convulsing while in exercise area. Upon exam, she had shallow breathing and was in intermittent lateral recumbancy. Second dog had a possible seizure. She became stiff legged and while trying to walk, she was very ataxic and fell over several times. She was removed her from the cage while still experiencing seizur-likee symptoms. She slowly had a decrease in the seizure activity and appears to be normal and comfortable. Both episodes lasted about 4 minutes. These clinical signs of very short duration did not repeat.

Study: #92
Animals: 12 Dogs
Type of Study: Oral Toxicity Study

Guidelines/Regulations:

- FDA
- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

Diagnosis: **Twelve Dogs** – Animals experienced intermittent or prolonged inappetence and weight loss. Supportive care was provided in the form of supplemental diet, IV therapy, nutria-cal, towels, water bowls and ice chips. These dogs were categorized as E as it was assumed that exposure to test article resulted in some level of discomfort/distress that resulted in the clinical signs observed.

Study: #93
Animals: 2 Dogs
Type of Study: Oral Tolerability and 10 Day Dose Toxicity Study

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies. This dose range study is being done to determine tolerability of test article and dosage selection for future studies that will be based on the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals. Without conduct of this study prior to the required full toxicity studies, larger numbers of animals may be needed for the full study.

- 21 CFR Part 312 IND application section 312.23 subpart B5 (ii)

- FDA

Diagnosis: **Two Dogs** – Animals experienced prolonged gastrointestinal upset. Supportive care was provided in the form of towels and water bowls.

Study: #94
Animals: 20 Dogs
Type of Study: 28 Day Oral gavage Toxicity Study with 14 Day Recovery

Guidelines/Regulations:

- FDA Redbook

- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

Diagnosis: **20 dogs** – Animal(s) experienced severe gastrointestinal upset, inappentence and weight loss. Supportive care was provided in the form of Nitrical, canned food, subcutaneous fluids and towels.

Study: #95
Animals: 7 Dogs
Type of Study: Oral Tolerability and 10 Day Dose Toxicity Study

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies. This dose range study is being done to determine tolerability of test article and dosage selection for future studies that will be based on the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals. Without conduct of this study prior to the required full toxicity studies, larger numbers of animals may be needed for the full study.

- 21 CFR Part 312 IND application section 312.23 subpart B5 (ii)

- FDA

Diagnosis: **Seven Dogs** – Castrointestinal upset (emesis/diarrhea/mucoid or soft stools), inappetence, acute weight loss and unexpected death. Supportive care was provided in the form of Nutrical, subcutaneous fluids and towels.

Study: #96
Animals: 2 Dogs

Type of Study: IV Toxicity Study

Guidelines/Regulations:

- FDA
- OECD
- MHLW

Diagnosis: **Two Dogs** – Animal #1758 had 16.5% weight loss from Day 1 to 8. Animal #1774 has 19.1% body weight loss from Day 1 to 22. Clinical signs of nasal discharge, cough, rales, dehydration and pale gums. Supportive care was provided in the form of Nutrical and Science Diet for inappentence and 0.9% NaC1 subcutaneous IV for dehydration.

Study: #97
Animals: 4 Dogs
Type of Study: IV Toxicity Study

Guidelines/Regulations:

- This study was conducted to support subsequent required regulatory studies. This dose range study is being done to determine tolerability of test article and dosage selection for future studies that will be based on the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals. Without conduct of this study prior to the required full toxicity studies, larger numbers of animals may be needed for the full study.

Diagnosis: **4 Dogs** – Multiple clinical signs consistent with anaphalactic response after injection. Duration of approximately 1 hour. Category E due to likely experienced some level of discomfort/distress associated with clinical signs.

Study: #98
Animals: 8 Dogs
Type of Study: IV Toxicity Study

Guidelines/Regulations:

- FDA Redbook 2000, DeGeorge, J.J., 1998
- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

Diagnosis: **Eight Dogs** – Body weight loss and clinical signs consisting of; red mucoid stools, red diarrhea, pale gums, dehydration, abnormal colored mucoid material. Dose levels were decreased to 7 mg/kg for both groups 4 and 5, Nutrical and subcutaneous fluids were administered as necessary.

Study: #99
Animals: 5 Dogs
Type of Study: 14 Day Oral Toxicity Study

Guidelines/Regulations:

- FDA Redbook
- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

Diagnosis: **- Five Dogs** – Dogs experienced seizure activity. Supportive care was provided in the form of towels to reduce the chance for stimulation post-dose.

Study: #100
Animals: 6 Dogs
Type of Study: Oral Toxicity Study

Guidelines/Regulations:

- FDA

- OECD
- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry, M3(R1) Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

Diagnosis: **Six Dogs** – Animals experienced prolonged gastrointestinal signs (inappetence, vomiting, diarrhea), excessive rapid weight loss. Supportive care in the form of nutritional supplements, fluid therapy, towels and heat lamps. Clinical signs were more severe than anticipated. All dogs were given a reduced dose for the remainder of the study and the dogs were placed on dosing holiday as needed. Dogs responded well to supportive care, euthanasia was not warranted.